KEY to the Biology Code

of the

CHEMICAL-BIOLOGICAL COORDINATION CENTER

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A manual for the use of the symbols of the Code, for coding results, procedures, and conditions of tests for biological responses to chemicals

Edited by
PHILIP G. SEITNER
in cooperation with
GEORGE A. LIVINGSTON and ANN S. WILLIAMS

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FOREWORD

This manual has been prepared as a guide to the use of symbols of the CBCC Biology Code for coding information about tests for biological responses to chemicals. It is also a description and explanation for each of the Code's parts.

The Key and Code must be regarded as a single unit. Their composition reflects the assumption that one volume will always be accompanied by the other.

The development and use of the Biology Code is discussed, against the background of the history, objectives, and procedures of the Chemical-Biological Coordination Center, in the Introduction and Appendix included with the Code. In that Introduction, the Key is described and the need for it is explained. In the Foreword to the Code, the definition of a field and the divisions of the Code into fields are explained; the major divisions of the Key follow those of the Code.

The frequency of cross references in the Key has demanded a standard nomenclature for its parts. In each field, the three major parts are referred to as sections; the sections, particularly the Specific Directions and Explanations Section of each field's description, are organized into numbered divisions, under some of which it has been convenient to make lettered sub-divisions.

The first section of each field describes such things as (1) the extent of the area of the field, in terms of the number of IBM punched card columns used, (2) the classification scheme of the items of the field, (3) the way symbols have been assigned or constructed according to the classification of the items, and (4) the number of items, of the particular category represented by the field, needed by the CBCC.

The second section of each field's discussion, General Use, describes briefly the nature of the items classified and coded in the field and the relationship of the field to all other fields relative to coding, as a whole, information from chemical-biological tests.

The final section is devoted to more specific details of directions and cautions for use of the code symbols and to explanations for coding patterns. In each field, the final divisions of this section indicate briefly what symbols are available for expansion of the field, whether the CBCC has established a special file of IBM punched cards arranged according to entries in the field, and whether more than a single code entry can be made in any of the code boxes of the Code Sheet (and consequently, whether only one or two or more separate symbols having distinct meanings can be punched in the same column of a single IBM punched card).

With regard to the structure of symbols, it will be discovered that within any given field, the code symbols are constructed according to a special pattern appropriate to the classification of the items of the field. Making the code symbols for the field actually represents a coding process for the items of that particular field, preliminary to and separate from the ultimate process of coding chemical-biological data using those previously prepared symbols. This process can be visualized as restricted to coding information about each item within a given field according to appropriate identifying criteria or indexes. In certain fields, the complexity and number of the items are such that this preliminary coding process, resulting in symbols for the field, demands special attention and considerable explanation. For example, in Field E, symbols for test organisms are constructed to carry specification of the phylum, class, order, family, and genus to which each species belongs. Likewise, in Field H, the symbols reflect the major system to which each specific organ of this list belongs. Any and all explanations for this process are part of that first Key section for each field.

Attention is called to Field E of the Code; it is seen to be composed of three separate parts for the three separate categories which can be coded in the Field. The three categories are (1) test organisms, (2) tumors, and (3) pathologies, one or the other of which represents the biological system treated (for the coding of which Field E is intended) in every chemical-biological test. Thus, Field E is made up of the Taxonomy (Test Organism) Code, Tumor Code, and Pathology Code. In the Key, separate sections have been appended for each of the Taxonomy Code, Tumor Code, and Pathology Code, explaining the information coded into the symbol for each organism, the symbol for each tumor, and the symbol for each pathology. These three sections are actually comparable to the initial (Organization) section of other fields; at the beginning of the General Discussion of Field E, the brief Organization section functions primarily to refer to the three later sections that substitute for it. In the General Discussion of Field E, prior to the three special sections just described, the section on Specific

Directions and Explanations is also divided exceptionally into five "Parts" for considering separately five subcategories of the major category of information represented in Field E.

Fields G-1 and G-2 have been discussed in the Key as a unit, since the same general type of information is coded in both fields and symbols used for coding in both fields are from the identical list in the Code. Distinguishing the uses of the two fields is also facilitated by discussing the two together. For the same reason, Fields H-1 and H-2 are described as a unit, as well as Fields S-1, S-2, and S-3.

Discussing Fields M and N as a unit is not due to their having an identical list of code symbols, but due to both fields being concerned with a similar type of information. The uses of the two fields can be distinguished more easily by considering them together. For the same reason, the descriptions of Fields W, X, and Y are presented essentially as a unit, though, like Fields M and N, each of Fields W, X, and Y has a different set of items and symbols in the Code.

Each of Fields T-1, T-2, and T-3 is discussed individually, even though all three deal generally with only a single category of information. Nevertheless, it has been convenient to introduce these three fields by a separate discussion of Field T, embodying explanation of the general objective shared by the three fields and general distinction in their use.

In all symbols of the Code to which reference is made in the Key, the capital letter O is indicated by the special symbol "Ø" to give it obvious distinction from the numerical zero.

For convenience, the term "double coding" has been used in the Key and Code with a limited definition; therefore, two symbols being entered in one column in one code line does not necessarily represent "double coding". The definition assigned to the term hinges on the evaluation of test results, ordinarily of two or more tests; in these tests, some condition of the test method differs (ordinarily, only one condition is involved), yet the test results are so nearly the same that the code evaluation of the biological response in both or all tests is by the identical symbol in Field Y. Both or all of such tests might be coded by a single code line in which the field coding the variable test condition (e.g., dose size, inoculum size, or route of administration) would have "double coded" the symbols for both or all of the variations of that condition (e.g., the range of doses or the various inoculum sizes or the various administration routes [Field M, Q, or S], giving test result evaluations indistinguishable by code in Field Y). Thus, "double coding" refers to the use of two symbols in one column representing variation in a single category of information.

In certain fields, symbols are provided for two different categories of information (e.g., Fields A, B, F, G, O, W) and, in these fields, the symbols of one information catetory (Symbol 0 of Field A, e.g.) can be entered in the same column of the same code line as symbols of the other category (symbols other than Symbol 0 of Field A, e.g.), whenever information of both categories is available for the test. These two entries in a single column, however, do not represent "double coding", as defined above.

In either case ("double coding" of the same category of information from two or more tests or the use of two or more symbols for two different categories of information in one test), the multiple coding of the column is punched on the same IBM card in that column.

However, fields for which the CBCC has established separate IBM punched card files ("filing fields", Fields D, E, H, I, J, T-2, and T-3) are never "double coded". Even if this were permitted, instructions would be given to punch two IBM cards, identical except in the field double coded on the Code Sheet. The reason for this is simply that a card is needed for each entry in one of these fields, in order to have the entry filed in the proper category.

The free use of underscoring in the Key perhaps needs some clarification. For some readers the underscoring may be distracting, but in general, the emphasis placed on a given word or phrase by an underscore has seemed to assist far more than to deter in extracting the intended meaning from explanations which have been sometimes difficult and necessarily complex.

(1) PHYSICAL STATE OF THE TEST COMPOUND

(2) INDICATION OF DIRECT, MASS APPLICATION VS. REMOTE, PARTICULATE APPLICATION (I. E , DISPERSION VS. APPLICATION OF THE UNDISPERSED COMPOUND)[1]

(3) INDICATION THAT INFORMATION ON CORRELATION OF ACTIVITY AND CHEMICAL STRUCTURES OCCURS IN THE DATA SOURCE

Organization

Organization of Field A is based on seven major items, represented by Symbols 1, 2, 3, 4, 5, 6, and 7. (Consult the Code for definitions of these symbols.) Each of these seven symbols is modified by IBM zone punches to form related symbols for indicating dispersion[1]. (See the explanation of the IBM card in the Appendix for the definition of zone punches.) For example, Symbol 2 (one punch only, in the 2 position on the IBM card) codes a liquid, pure compound, applied undispersed; Symbol B (two punches on the IBM card in Column 9: one in the 2 position and one in the 12 zone punch) codes a liquid, pure compound, applied as a spray; Symbol K (two punches in Column 9: one in the 2 position and one in the 11 zone punch) codes a liquid, pure compound, applied as a mist or aerosol. Thus, one punch is provided (in the 2 position) common to all three of these code units so that if in a file it were important to be able to sort out all liquid, pure compounds, it might be done with a single sort on that common punch.

General Use

In Field A is coded the state of the test compound at the time of its introduction to the biological component or components; this is consistent with the coding of all other fields dealing with the application of the chemical (Fields B, C, M, N, O, P, and S-3) in which application is also described in terms of the conditions existing at the time of application to the organism to which direct application is made, whether it is the host organism or the test organism.

Ordinarily, the presence of a host coded in Field J implies application being made directly to that host; therefore, all coding of conditions of application refers to that direct application to that host and no coding implication is made as to the condition of the test compound when it reaches the test organism. (Only two exceptions are made. When, for clarity of a coded statement, there is coded in Field J an inanimate, liquid [or semi-liquid] environment as a host [in essence, a solvent or vehicle] in which the test compound is dispersed, coding of application, in Fields A, B, C, M, N, O, P, and S-3, describes application to the test organism. The second exception is described in Division 3 of the Specific Directions and Explanations below.)

The dispersing of a compound in applying it may appear to be a manner of application, the coding of which has been assigned to Field S-3. However, distinction between the second use of Field A (indicating whether the compound is applied dispersed or undispersed) and the use of Field S-3 can be understood by examination of the two fields. Field A is concerned with describing the compound that is being administered and is particularly concerned with the condition of that compound when introduced to the animal or plant. Coding the compound's being mechanically dispersed as a spray or aerosol is as much a description of its condition as is the coding of its being a liquid or a solid or dissolved, etc.

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[1] "Dispersion" is used here to mean scattering the test material by use of a sprayer, atomizer, duster, aerosol; "dispersion" is NOT used in Field A definitions of the Code to describe mechanical spreading or smearing of the test material over the surface of--or diffusing through the substance of--a test organism or host. An examination of the Code terms will clarify this.

Field S-3, on the other hand, has as its objective the description of the route of the test compound to or into the animal or plant, regardless of the condition of the compound. It is true that certain routes would not be practical for all states in which the compound might be; nevertheless, the use of Field S excludes any actual description of the condition of the compound--except by implication in specifying the route (e.g., specifying in Field S "fumigation" or "inhalation" which implies application of a compound as a mist or aerosol, but which makes no pretense at actually expressing by code that condition of the compound). This is discussed also in Division 4 of the Specific Directions and Explanations for Field S-3.

The third distinct use of Field A is discussed in Division 8 below. It is a means of retrieving from the file of coded data those Biology Code Sheets containing literature (or other) references in which the author has made observations on correlation of chemical structures and biological response to those chemicals. The observations themselves are not coded nor are the details included in the Code Sheet's written abstract of Field A; there is merely the coded indication in Field A that the information can be found in the reference. In the written abstract portion of Field A, only a brief synopsis is made of the specific correlations the author discusses in the article.

Specific Directions and Explanations

1. Coding in Field A when the test compound is applied to the test organism

When the test compound is applied directly to the test organism in Field E (and when there is no host coded in Field J), use the code symbol best describing the state of the test compound at the time of application to the test organism.

2. Coding in Field A when the test compound is applied to the host organism

When the test compound is applied directly to the host ORGANISM (Field J) in or on which is located the test organism (Field E), use the code symbol best describing the state of the test compound at the time of application to the host. (See Division 5 for an exception, related to NON-LIVING hosts.)

3. Coding in Field A when the test compound is applied DIRECTLY to the test organism, even when it is on or in a host

When the test compound is applied directly to the test organism (Field E) on or in a host (Field J) (e.g., applied by dropping it on a tick attached to a dog or injecting it into a tapeworm cyst in a rabbit), use the code symbol best describing the state of the test compound at the time of application to the test organism.

4. Coding in Field A when the test compound is applied to a host prior to inoculation with the test organism

When the test compound is applied to a host (or environment), coded in Field J, prior to the introduction of the test organism, use the term which describes the state at the time of application to the host, regardless of the state at the time the test organism is introduced. (See the following division for an exception.)

5. Coding in Field A when the test compound is applied to a non-living host

The provisions for application to hosts (Divisions 2 and 4 above) have as an exception the situation in which the test organism is added to water, saline, or nutrient media, for example (i.e., inanimate, liquid or semi-liquid hosts or host environments coded in Field J), in which the pure test compound (liquid, gas, or solid) has been dispersed in amounts to bring it to the test concentration as coded in Fields M and N (by dissolution, emulsification, suspension, or mechanical mixing). In this case, the host coded in Field J is the solvent or vehicle which is under other circumstances always coded in Field C; the CBCC has not coded Field C in such instances--not necessarily because it would represent coding duplication with Field J, but because many of the specific materials such as culture media have not been included as items of Field C. Field C could be coded, if this host in Field J happens to be also one of the specific items of Field C. Since coding Field A with liquid, gas, or

solid (the state prior to introduction into the water, saline, etc.) would not serve any useful purpose in this situation, this field should be coded with the state of the compound in the host water or nutrient (i.e., the state as applied to the test organism) rather than with the state when added to those hosts.

6. Coding in Field A when the test compound has been applied to a surface as a residue

Occasionally, a test compound is introduced onto a surface (or in a cloth, filter paper, etc.) in an organic solvent, for example, which is subsequently allowed to evaporate, leaving the test compound as a residue. (I) If the technique dictates that the test organism is then exposed to the residue, Field A is correctly coded with the state when applied to the surface, according to Division 4 above. (II) However, if this treated surface (e.g., an aquarium inner surface, microscope depression slide, Petri dish, a filter paper disc, etc.) is then immersed in water, for a test with aquatic organisms, "water" is to be coded in Field J, nothing need be coded in Field C, and Field A is to be coded only if it is known or stated that the compound is completely soluble in water; otherwise, Field A will be left uncoded.

7. Coding in Field A when the test compound is a gas

If the test compound is administered as a gas and its concentration is expressed by the author only in terms of this gas (e.g., per cent test gas in N, O_2, or air) which is subsequently streamed through (1) a bath or perfusate of an organ, tissue, or immersed organism, or (2) a suspending medium of a tissue macerate or an enzyme-containing secretion (e.g., milk), the concentration of the test compound in the gas will be coded in Field M. Therefore, in this case, Field A must be coded with "gas", Symbol 1, and Field C need not be coded, since the suspending solvent is implied in coding the preparation as a homogenate (Field G) or secretion (Field I) or in coding the diluent of the homogenate (Field J). Note, however, that if the author should actually have determined the dissolved concentration of the test compound, coding in Fields M and C should be based on that concentration and solvent and Field A should be coded with "solution", Symbol 4.

8. Indication of information on correlation between chemical structure and biological activity

The Symbol 0 is used (either alone or with one of the symbols for physical state) to indicate that the article contains information on correlation of chemical structure and biological response. The information may deal only with the compound under test or with a series of which the test compound is a part. When an article contains information about the relationship of chemical structure to a certain biological effect, Symbol 0 should be coded in Field A in each code line which describes that effect (Field T) for all the compounds whose chemical structure is discussed. Symbol 0 should not be coded in lines for other actions which happen to be in the article but for which the relationship to chemical structure is not discussed.

When using Symbol 0, it is necessary to give some idea, in the language portion of the code line, of the information contained in the article. Do not write merely, "structure-activity"; write (e.g.), "activity of α, β, γ isomers studied" or "effect of methyl, propyl groups studied".

9. The nature of items 2, B, K, 3, and C

Note that Symbols 2, B, K, 3, and C refer to undiluted compounds.

10. Symbols available for additional items of Field A

The following symbols have not been used and are available for items of Field A: 8, 9, H, I, J, L, P, Q, and R. Symbols S through Z are not available, because the IBM 0 zone punch has been used as a special symbol. If the available symbols are used to conform to the established organization of the field, Symbol J should be used for a gaseous state as are Symbols 1 and A; Symbol L should be used for a state of an undiluted solid compound as are Symbols 3 and C; and Symbol P should be used for a suspension-in-a-solid state as are Symbols 7 and G. The six remaining symbols can form two new groups: (1) 8, H, and Q and (2) 9, I, and R.

11. File of coded biology data on IBM punched cards arranged according to symbols for states of chemical compounds

The CBCC has established no separate file of coded biology data on IBM punched cards arranged by Field A entries.

12. Double coding in Field A

If several tests are run, with the only difference in the tests being the state of the test compound, and the results are so similar that all the tests would be coded identically in every coding field except Field A, the tests are NOT to be all combined into a single code line with all the states used coded (i.e., double coded) in Field A. The CBCC has refrained from this partly because the double punching of letter symbols and numerical symbols (both of which are in Field A) is not possible (though actually any of Symbols 1-9 could be double coded) and partly because the state is so intimately associated with solvents, carriers, and conditioning agents (i.e., Fields B and C) that it is improbable that the difference in such tests would involve only Field A, but would also involve Fields B and C. The mechanics of double coding all of Fields A, B, and C, therefore, represents more confusion and difficulty than would be justified for those particular coding fields. For these reasons, the CBCC prefers to simplify coding procedure by the policy of never double coding in Field A, even if it makes necessary coding two or more lines for tests identical in results and procedure except for the state of the compound. (Field A can have two entries in the special case of using Symbol 0 with a symbol for the state of the compound, but this does not represent double coding as it is described above. If Symbol 0 is used with another symbol in Column 9, both symbols are punched in that column on a single IBM card).

(1) CONDITIONING AGENT

(2) MISCELLANEOUS INFORMATION ABOUT THE TEST COMPOUND ADMINISTRATION

(3) INDICATION THAT IN THE DATA SOURCE THERE IS INFORMATION ON THE EFFECT OF pH ON THE CHEMICAL ACTION

General Use

This field is principally for recording the presence of inert materials which are administered, with the test compound and its solvent or vehicle, for providing increased viscosity, facilitating emulsification or spreading, etc.

In general, when a material regarded as an inert conditioning agent is administered with the test compound, it is adequate merely to code the fact of its presence, rather than attempt to assign code symbols to each agent or to each type of agent. Symbol 1 is used for this purpose.

However, symbols have been given to a number of specific materials used very frequently for changing viscosity or imparting physical stability of a preparation. Note that in this field, coding of agar or gelatin, for example, is not a record of any use of the materials as biological culture media ingredients, but describes exclusively their use in conditioning test compound preparations.

Field B has afforded space for making a coded record of certain information relevant to the conditions of administration, which may affect the interpretation of the coded line (e. g., administration of mixtures or precursors).

Finally, a symbol has been provided to permit recovery of all references with information on specific effects of pH on biological responses.

Specific Directions and Explanations

1. Information about influence of pH on the test compound's action on the test organism

Symbol 9 in Field B is used to indicate that the article from which the data were taken contains information on the effect of pH on the effect of the test compound coded in Fields T-1 and T-2.

2. Use of Symbol 7; administration of the test compound as its precursor

Symbol 7 should be used only when it has been demonstrated that the predecessor of the test compound is converted to the test compound and does not itself affect the action coded in Fields T-1 and T-2. Under the conditions when Symbol 7 can be used, a separate Code Sheet is always made for the administered compound, on which Field B is not coded with Symbol 7, recording the administered compound's conversion (Symbol Series FE--, Field T-2). Unless definite evidence is given by the author that the administered compound is inactive (relative to the action coded in Fields T-1 and T-2) and that its conversion product is active, that conversion product can not be coded as a test compound with Symbol 7 in Field B. When such evidence is lacking or even if it is well known by the coder but not so described by the author, the action must be coded only as being that of the compound administered (i. e., as being the result of administering that compound). The symbol is useful mostly in coding distribution studies (Symbol Series F9-- and FA--, e. g., of Field T-2) when the compound deposited and measured is shown to be a derivative of the compound administered and concentration is expressed in terms of the derivative.

Example: Penicillin is more highly concentrated in lung tissue when introduced as Leocillin (from which penicillin is biologically derived by degradation) than when penicillin is itself administered. To record that penicillin is deposited in greatest

amounts when administered as a given dose of Leocillin, penicillin is treated by the coder as the test compound and Field B is coded with Symbol 7 to record that the compound was administered as a dose of a precursor (Leocillin), coded in Fields M or N. On a separate code sheet for Leocillin, the conversion of this compound to penicillin is coded.

3. Formulations[1]

Symbol 6 is a provision for coding the fact that the test compound is administered as an ingredient of a formulation. A formulation is defined as a product containing a given proportion of the test compound, the remaining ingredients being disregarded and presumably inert. Symbol 6 accommodates only cases in which the action is attributed to a single ingredient. The coded dose of such a formulation should be the calculated amount of the test compound. When the author specifically states that he is administering mixtures of two or more compounds, any of which is being tested as an antagonist, synergist, or simulant for any one of the others, none of the compounds is to be coded except by the procedure described in Division 5 below. The percentage of the test compound in the formulation administered or the percentage purity (which percentage values have been used in calculating the dose coded in Fields M and N) should be given in the written abstract portion of Field B with the name of the formulation, if given by the author. Do not place the formulation name or the per cent purity on the chemistry side of the Code Sheet; place there only the test compound name. The CBCC policy has been to admit few data from tests using formulations.

4. Mixtures[1]

Symbol 0 is provided to allow, when it is so desired, the coding of data from tests in which a mixture of compounds is administered, the results of the test not being attributable to any one compound of the mixture. In such a case, the mixture is not assigned a unique Chemical Serial Number; instead, the data are recorded first on a Code Sheet for one of the compounds, with Symbol 0 coded in Field B. Unless there is reason to do otherwise, the line must be duplicated on separate Sheets for each compound of the mixture. In coding test compound mixtures, the dose coded is expressed in terms of the total mixture.

In selecting chemical-biological test data, the CBCC has seldom elected to include data from tests of chemical mixtures. Mixtures, as discussed here, exclude cases in which there are given data for each of the mixture's compounds tested separately so that the results can be interpreted in terms of synergism, antagonism, or additive effects.

5. Symbols available for additional items of Field B

Symbol 8 and all letter symbols, with the exception of letters F, G, I, Ø, P, R, and S through Z may be used for additional items of Field B. (Letters S-Z are unavailable by having used the IBM 0 zone punch as a symbol and the other six letters are unavailable because Symbols 6, 7, and 9 can be double punched with any one of Symbols 1, 2, 3, 4, 5, and 9).

6. File of coded biology data arranged according to symbols for conditioning agents

No separate file of coded biology data on IBM punched cards, arranged by Field B entries, is maintained by the CBCC.

7. Double coding in Field B, as distinguished from coding of two types of information in Field B in the same line

The CBCC has not double-coded two or more conditioning agents used in separate test runs, for the same general reasons as given for not double-coding two or more states of the test compound in Field A. (See the last division of the Specific Directions and Explanations section for Field A.)

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[1] Note that the definitions of "formulation" and "mixture of compounds" do not include the mixture of isomeric forms of a compound; the latter would be regarded chemically as a single compound for coding purposes.

Any of Symbols 9, 6, 7, or 0, each of which codes unique information other than conditioning agents, can be coded in the same code line (and punched on the same IBM card) with any of the code symbols for conditioning agents (Symbols 1, 2, 3, 4, and 5).

SOLVENT OR VEHICLE

Organization

The items of Field C are solvents and vehicles which have been encountered during the period of CBCC coding. The list has been found generally adequate, but there remain 11 symbols (exclusive of zone punches which may be used alone) available for additions. For this edition, the solvents have been arranged by alphabetical sequence.

Only liquids (or solids such as fats, with melting points fairly close to room temperature) have been included in Field C. Solids (charcoal, Bentonite, talcum, solid foods, etc.) are considered merely "fillers", are assumed to be inert, and are not materials that can "carry" the test compound to or into the test organism in the same sense that liquid materials are "carriers". The fact that the test compound may be diluted by a solid "filler" is indicated by appropriate coding in Field A rather than Field C and in the written abstract of the Code Sheet.

General Use

Solvents or vehicles are expressed in Field C. The purpose of the field is not primarily to record the solubility property of the test compound (which information is more appropriate on the chemistry records), but to record the material in which the compound is distributed. By virtue of being the material "carrying" the test compound to or into the test organism, the solvent or vehicle used and its relative efficiency may be most significant in the outcome of a test.

Specific Directions and Explanations

1. The test compound in a non-living host or host environment coded in Field J

When the test compound is dissolved or suspended in a culture medium or solution coded in Field J as the test environment, it is not necessary to code anything in Field C.

As a result of such applications to the habitat or culture medium coded in Field J, the test compound diffuses through the host and reaches the test organism in a lower concentration than that applied to the host. If the concentration after such dilution is known, that is preferably the dosage coded in Fields M and N. For coding of this dosage and Field C, consult Fields M and N, Specific Directions and Explanations section, Division 7.

2. Solvent MIXTURES; solvents and VEHICLES; STOCK SOLUTION solvents; solvents EVAPORATED to leave residues of the test compound

If more than one solvent is present (e.g., 95% alcohol and 5% water or 75% acetone and 25% alcohol), one of the following procedures is used:

(a) When solvent mixtures are present, do not attempt to code any specific solvent. Code "mixture", Symbol A.

(b) When both a solvent and a vehicle occur (as in emulsions, in which a compound is dissolved in a solvent which is emulsified in the vehicle), code the continuous phase, i.e., the vehicle (the substance that "carries" the compound and its solvent to or into the test organism), in Field C. The actual solvent of the test compound is to be recorded in the written abstract portion of Field C.

(c) Compounds are frequently dissolved in alcohol, acetone, or other solvent to provide a stock solution from which a given dilution is made with water, particularly in tests with aquatic organisms (fish, snails, etc.). In such cases, the aqueous diluent is coded in Field C, with Symbol R.

(d) When a test compound, dissolved or suspended in water or any other solvent, is applied to a surface which is subsequently dried to give a test compound residue, followed by submergence of the surface in water for exposure of aquatic organisms (in which case "water" would be the host coded in Field J), Field C is not coded. See Division 5 of Specific Directions and Explanations for Field A for this coding procedure.

3. Symbol 1 may be used to indicate NON-NEUTRALITY (pH acidic or basic) of an AQUEOUS solvent

The acidic and basic solutions included in the definition for Symbol 1 refer ONLY to aqueous solutions. The symbol is not intended for unadulterated acids or bases as solvents (e.g., lactic acid).

4. Symbols available for additional items of Field C

Symbols 8, C, D, E, F, J, L, V, X, Y, and Z are available for additional items for Field C.

5. File of coded biology data on IBM punched cards arranged according to symbols for solvents

The CBCC has established no separate file of biology data arranged by Field C entries.

6. Double coding in Field C

When experiments, performed with a given test compound, are repeated using different solvents and the results differ in a degree that can be distinguished by code in the evaluation fields or in the action fields, separate lines should be coded to record the influence of the solvent. If the results are so nearly alike that they can not be distinguished by code in Field Y, only a single line, with a single solvent coded in Field C, should be constructed, with the remaining data of the other tests entered in the written abstract (i.e., Field C should not be double coded).

FIELD D
Columns 12, 13, 14,
15, 16, and 17

SECONDARY COMPOUND

Organization

In this field, six IBM punched card columns are provided for entering the Serial Number of a chemical compound. The basic CBCC Chemical Serial Number consists of six units (six letters or numbers); however, there is in addition a 2-unit system for designation of salts and radioactivity. Since there is not sufficient space in this 6-column secondary compound field for entering the two final units indicating a salt or specific radioactivity, the latter information, when known, must be included in the written abstract portion of the field. In the following descriptions, "coding" a secondary compound in Field D refers to the use of the compound's Serial Number as a code symbol, not to the structural coding which is found only in the Chemistry Files.

General Use

Field D is used for coding a compound other than the test compound (i. e., it is for coding a "secondary" compound).

Coding a compound in Field D is restricted to instances when any of certain specific relationships exist between the action of a test compound and another (a "secondary") compound. These circumstances under which Field D is coded are indicated in the definitions of the code symbols of other fields; therefore, Field D is never coded unless there are specific directions, with the code symbol of some other field, to code a compound in Field D. The four general uses of Field D are listed at the end of this section.

In a case when it is appropriate to use Field D, the name of the compound and the structural formula are written on the Code Sheet, in the written abstract portion of the field. It is essential to indicate all double bonds, group positions, etc., in full. Do not use abbreviations, such as PABA for para-aminobenzoic acid, if the full name is given in the paper.

The coding of the compound requires that the coder have access to the CBCC Chemistry Index Card File arranged alphabetically by name; on each card of this file is the basic six-unit CBCC Serial Number assigned to the compound represented on the card. If this file is not available to the coder, Field D must be left uncoded and the code boxes left open for filling in by someone who does have access to the Chemistry Index Card File. In this case, however, the coder must always have completed the written abstract for the field as well as any of the three special code designations in Column 16 or 17, when the latter are appropriate. (See Divisions 3, 4, 5, 10A, and 10B, in the following section, Specific Directions and Explanations, relative to these special symbols.)

Field D is used to express:

1. A compound whose action is synergized or potentiated (Field T-1, 8); antagonized, neutralized, or antidoted (Field T-1, 9); simulated or replaced (Field T-1, A) by the test compound; or additive with the test compound (Field T-1, C).

2. A compound, naturally occurring or administered, whose uptake (Field T-2, F6--), synthesis (Field T-2, F8--), distribution (Field T-2, F9--), storage or concentration (Field T-2, FA--), absorption (Field T-2, FB--), excretion (Field T-2, FC--), ability to permeate (Field T-2, FG--), incorporation (Field T-2, FH--), withdrawal (Field T-2, FI--), alteration (Field T-2, FE--), or elimination (Field T-2, FF--) is affected by the test compound.

3. A compound which serves as a standard for comparison with the test compound (Field X, Criterion 03 or 04). (This use of the field is distinguished by coding an asterisk in Column 17.)

4. A compound to which cross tolerance or cross tachyphylaxis, is produced by administration of the test compound. (See Symbols 514 and 5131 in Field T-2.)

Specific Directions and Explanations

1. Use of Field D is determined and directed by other fields of the Code

As explained above, under "General Use", Field D is coded only when the definition of a symbol in another field of the Code specifically directs the coder to do so; these specific uses of Field D are described in subsequent divisions.

2. Field D can never have more than one compound coded in any one line

Double coding (i. e., coding two compounds) in Field D is never permitted, because it is impossible to designate, in any way that will distinguish them, more than a single compound in a given field on an IBM punched card. Therefore, in a situation where two (or more) secondary compounds, each administered with the test compound in independent tests, are found to have their actions affected by the test compound to so nearly the same degree that the coding of the data would be identical for both of the compounds (except for coding in Field D), Field D can not be double coded with all of the secondary compounds to condense the data into a single line. A separate line must be coded for each secondary compound, even though the code lines are identical except for Field D.

3. Two or more secondary compounds, all essential and all administered together; Symbol # in Column 16

Occasionally, data are encountered in which the test compound is tested for an effect on the action of two or more essential secondary compounds administered together, (i. e., the action of the secondary compounds would not occur if one of them were absent) rather than on the action of a single secondary compound. (Note that this does not refer to mere mixtures of secondary compounds, any one compound of which may produce the action; mixtures are seldom, if ever, coded in Field D by the CBCC.) In this situation, the two or more secondary compounds are all essential components of a single test (in contrast to the situation described in Division 2 above, where the two or more secondary compounds bear relationship to the action of the test compound through independent tests). Since Field D can be coded with but a single chemical and since it is important that there be coded all of those secondary compounds that produce together the action affected by the test compound, A CODE LINE IS PREPARED FOR EACH MEMBER OF THE SECONDARY COMPOUND COMBINATION, all the lines being identical except for Field D. As a means of relating these lines and indicating by code the situation just described, SYMBOL # IS PLACED IN COLUMN 16 of each of these related lines; Symbol # is used in Column 16 ONLY in coding this situation. Place this symbol at the top of the code box so that room is left in the box for the entry of the fifth unit of the compound's symbol.

4. Standard of comparison coded as a secondary compound; Symbol * in Column 17

To designate that a compound is used as a standard for comparison in evaluating the test compound action, place Symbol * in Column 17. Place this asterisk at the top of the code box so that room is left for the entry of the sixth unit of the compound's symbol in the box. The presence of an asterisk in this column indicates that the secondary compound is known to produce the action coded in Field T-2 when tested alone and the degree of action of the test compound is evaluated by comparison to the known degree of action of the secondary compound; it distinguishes this use of Field D from the other uses of the field.

5. Radioactivity of the secondary compound; Symbol * in Column 16

To designate that the secondary compound is radioactive, enter Symbol * in Column 16. Place this symbol at the top of the code box so that room is left for the entry of the fifth unit of the compound's symbol in the box. Note that the asterisk in Column 16 merely gives added information about a special property of the secondary compound. It does not affect the interpretation that the test compound alters

the action, coded in Field T-2, produced by the secondary compound; i. e., it does not signify a special use for Field D as does an asterisk in Column 17 (see Division 4).

6. Data from tests using secondary compounds of uncertain identity are coded only exceptionally

Test data involving secondary compounds that are ill-defined have not ordinarily been selected for inclusion in the CBCC files, just as data involving test compounds of uncertain identity have seldom been selected. For example, data involving materials such as natural or synthetic mixtures, extracts, vaccines, etc. have seldom been coded. Occasionally, exceptions have been made and such data are coded, necessitating classifying and assigning a CBCC designation to the material coded as a secondary compound. Materials known to be discrete chemicals have more frequently been given CBCC Serial Numbers than have extracts, vaccines, natural product mixtures, etc., even though the lack of knowledge of their structures makes their processing irregular. In Field D, coding of materials of uncertain identity must be, for each case, the result of special deliberation and a decision, in order to bestow on that material recognition as a distinct chemistry file entry with a unique reference number.

7. Enzymes are NOT CODED IN FIELD D as secondary compounds when their BIOLOGICAL ACTIONS are affected by test compounds; however, if their metabolic fate is affected by the test compound, as indicated in Field T-2, they can be coded as secondary compounds in Field D

The coding of a test compound's effect on the activity of an enzyme deviates slightly from the usual procedure of coding in Field D the compound whose activity is affected by the test compound. It will be noted that the Code provides for enzymes being coded in Field T-2, symbol series 7---; therefore, the purpose that would be served by placing this "secondary" compound, the enzyme, in Field D is satisfied by the entry in Field T-2 and placing it in Field D as well as in Field T-2 would be not only unnecessary but confusing to the interpretation of the code line.

Therefore, when a test compound (1) has an effect on the action of an enzyme (e. g., inhibits or enhances an enzyme's action) or (2) has an effect on the action of a secondary compound which in turn affects an enzyme action (e. g., antagonizes, synergizes, or simulates the secondary compound's action on an enzyme action) or (3) is a coenzyme for an enzyme action, the enzyme is always coded in Field T-2 and never in Field D, even though it is in a sense a secondary compound.

In contrast to this, when there is not being coded the test compound's effect on an enzyme action, but the test compound's effect on an enzyme's synthesis, destruction, excretion, etc. (Field T-2, Symbols F8--, FE--, FF--, etc.), the enzyme is written and its CBCC serial number (not its Field T-2 symbol) is coded in Field D.

The SUBSTRATE of an enzyme affected by a test compound is never to be considered as a secondary compound and is never coded in Field D.

8. A carcinogen that produced a tumor being treated is not a secondary compound

In the case of coding the action of a test compound (which is not being tested as a carcinogen) on a tumor which was induced by a carcinogen, the carcinogen is not to be considered as a secondary compound and is therefore not to be coded in Field D. The description, origin, or source of the tumor is coded by Symbols S through Z in Field F.

9. The action of the secondary compound can not be coded

When Field D is used to code a compound whose action is synergized, antagonized, or simulated by the test compound or is additive with the action of the test compound (see the first of the four uses itemized under the section on General Use), this is indicated by the Symbols 8, 9, A, or C of Field T-1. Note that it is the secondary compound's action that is affected by the test compound and it is the biological state, quality, or process on which the secondary compound acts that is coded in Field T-2. It is impossible to code the action of the secondary compound (Symbols 1, 2, 3, e. g.), because Field T-1 must be used for the test compound's effect on the action (Symbols 8, 9, A, or C). Ideally, there should be a second Field T-1 for coding the action of a secondary

compound, but the CBCC has not made this provision. Therefore, this action of the secondary compound must always be included in the written abstract portion for Field T-2 and whenever a secondary compound's action is synergized, antagonized, or simulated by or is additive with the test compound, the written abstract on the code sheet must be consulted to understand the action of the secondary compound which has been affected, as indicated in Field T-1, by the test compound.

10. Procedures when conflicts occur in the use of Field D

Ideally, a special coding field would be established for each of the four uses for a secondary compound listed in the General Use section. Then, if a test technique involved two of those aspects (e.g., antagonism evaluated by comparison to a standard), each could be indicated in its respective position on the Code Sheet and IBM punched card. The great infrequency of tests in which this occurs, however, makes impractical reserving so many IBM columns (12 columns for two of the uses or 24 columns for all four uses of secondary compounds). For this reason, only the single field of 6 columns has been reserved for any one of four possible uses. As a result, when occasionally test data involve two secondary compounds used in two of the four possible ways, having only one field, Field D, for all the uses of secondary compound poses a problem of competition for the field. The competition occurs with at least four general situations. These are described below as Conflicts A, B, C, and D, with an explanation of CBCC procedure for each case.

A. When there is an antagonized, synergized, or simulated compound or a compound whose action is additive with the test compound (i.e., a Field D entry called for by Field T-1, Symbols 8, 9, A, or C) and the metabolism section of Field T-2 (Symbols F6--, F8--, F9--, etc.) calls for the entry of a compound in Field D.

   In this case, the compound antagonized, synergized, or simulated or the compound whose action is additive with that of the test compound (Field T-1) is coded in Field D.

   The compound called for by Field T-2 is merely written on the Code Sheet, in the written abstract portion of Field T-2; the general class to which the compound belongs (i.e., --1 to --G under Symbols F6--, F8--, etc., and ---1 to ---L under Symbols FF1- to FFD-) is coded in Field T-2 in the usual way. That compound written in Field T-2 is not coded in Field D nor anywhere else. The code line will then state that the test compound antagonizes (or synergizes or simulates) the secondary compound's effect on the metabolism as coded in Field T-2. Note that the written description in Field T-2 must include the secondary compound's action, since there is no way to code this (inasmuch as Field T-1 is occupied with the action of the test compound, as explained above in Division 9).

B. When there is an antagonized or synergized compound or a compound whose action is additive with the test compound or which the test compound simulates (i.e., a compound in Field D called for by Field T-1 Symbols 8, 9, A, or C) and the evaluation of the action is made by comparison with a standard (Field X, Symbols 03 or 04) which must also be in Field D.

   Two lines must be coded, if the action is positive.

   The first line is coded with the symbol for "antagonizes" (or "synergizes") in Field T-1 and with the antagonized (or synergized) compound in Field D; the criterion of evaluation for this line must be "Author's Evaluation", Field X, Symbol 01.

   The second line is also coded with the symbol for "antagonizes" (or "synergizes") in Field T-1 and the standard compound, to which the test compound is compared for evaluation, is coded in Field D (including an asterisk in Column 17); the criterion for evaluation is either 03 or 04 of Field X. If the action is negative, this second line is not required.

C. Symbol FF-G of Field T-2: When there is a test compound which has an effect on the elimination of a metabolite of a compound and the metabolite is named. For example: The test compound causes an increase in urinary excretion of the metabolic product (Compound Y) of Compound X. (In this example, Compounds X and Y vie for a place in Field D, since Symbol FF1G [metabolite of the chemical specified in Field D] requires Compound X being in Field D and general directions require that the identity of the metabolic product [Compound Y] be coded in Field D when known.)

The parent compound is coded in Field D. In Field T-2, ---G is coded with whichever of Symbols FF1- to FFD- is appropriate (in the example above, FF1G); in the written abstract portion of Field T-2, the name of the metabolite is only written and is coded nowhere.

A second line is not coded to indicate the action of the test compound on the elimination of the metabolite (which would provide a line with the metabolite coded in Field D), since the specification for coding the metabolite in Field D is merely a matter of adding supplementary information when it is known; the code name of the metabolite is not actually essential to the interpretation of the coded action of the test compound.

D. When the test compound has an effect on the nutrient uptake, chemosynthesis, distribution, etc. (i.e., Field T-2, Symbols F6--, F8--, etc.), of a secondary compound whose name is specified and the action is evaluated by comparison with a standard. E. g.: The test compound causes an increase in absorption of Vitamin C, the degree of increase being evaluated by comparison to the increase caused by a standard, Compound X. (Since the vitamin is specified as Vitamin C, Vitamin C should be coded in Field D; however, the standard compound should also be in Field D.)

Two lines are to be coded, if the action is positive.

In the first line, place in Field D the compound whose nutrient uptake, chemosynthesis, distribution, etc., is affected. Evaluate the effectiveness by the Grid (percentage increase or decrease) or, if the actual control value and value following treatment are not reported, evaluate by Criterion 01 of Field X with an evaluation 0 or 1 in Field Y. In any case, do not use Criterion 03 or 04.

Code the second line to be like the first line in all fields except Field D and the evaluation fields; use Criterion 03 or 04 and code the standard compound in Field D, adding Symbol * (representing the IBM 12 zone punch) in Column 17.

In summary, it will be noted that the resolution of the conflicts reflects a precedence given to coding in Field D compounds whose actions have been affected by the test compound, as indicated by Symbols 8, 9, A, and C in Field T-1; such secondary compounds are always coded. (See Conflicts A and B.) Second in the scale of precedence is the coding of compounds used as standards of comparison to the test compound; the CBCC also always codes the standard of comparison, even when a second code line is necessary to code a standard used to evaluate the effect of the test compound on the action of a secondary compound, using Symbol * in Column 17 of the line coding the standard compound in Field D. (See Conflicts B and D.) Last in the list is the coding of compounds whose metabolic fate is affected--or compounds to which tolerance/sensitization is produced--by the test compound, indicated by certain symbols of Field T-2; if this last use conflicts with either of the first two major uses above, the CBCC prefers omitting coding the compound called for by Field T-2 on the grounds that it is of least importance. (See Conflict A.) In view of this, retrieval of all compounds whose metabolic fate is affected (as indicated by coding in Field T-2) can not be accomplished by sorting in Field D for coded biology data. (The only practical way of finding these would be by selecting IBM cards with the particular symbol or symbols in Field T-2 and sorting for Symbols 8, 9, A, or C in Field T-1 and for a 12 zone punch in Column 17 of Field D; if none of these symbols of Fields T-1 and D are on the cards, coding in Field D on all the IBM cards at hand is of compounds

related to the particular Field T-2 symbols, but if any of these symbols of Fields T-1 and D are on any of the cards, reference must be made to the code sheets corresponding to these cards to learn the identity of the compound related to the Field T-2 symbol.)

The only alternatives to the procedure which involves the conflicts in Field D as described would be to omit coding of all but one of the major units of information (i.e., all but one of the four uses of Field D as described in the section General Use) or to provide as many fields for secondary compounds as there are uses now for Field D. Neither of these has been practical for the CBCC and the present multiple use of a single field has been largely satisfactory, in spite of occasional conflicts and slightly greater complexity of use.

11. File of coded biology data on IBM punched cards arranged according to symbols for secondary compounds

The CBCC maintains a separate file of all coded biology data (i.e., all IBM biology punched cards) in which Field D has been coded, arranged by Field D entries. Thus, there are quickly retrievable biology data for any compound, or for all compounds, which have in some way been affected by test compounds or which have served as standards of comparison to the test compound. The latter are easily distinguished by the IBM 12 zone punch in Column 17. Further, after removing all cards with secondary compounds that are standards of comparison, the remaining cards can be sorted by Symbols 8, 9, A, and C in Field T-1, distinguishing the secondary compounds whose action has been affected by the test compound from those whose metabolic fate has been affected. These are simple and rapid card sorts, insignificant in terms of time and effort compared to the very large sort necessary to retrieve secondary compounds if a special file of biology data with Field D coding were not available.

12. Double Coding in Field D

Double coding is not permitted in Field D. However, Symbol # or * in Column 16 or Symbol * in Column 17 may be coded, in addition to the symbol for the single secondary compound, and both are punched on the same IBM card.

FIELD E
Columns 18, 19, 20, 21,
22, 23, 24, and 25

ORGANISM, TUMOR OR PATHOLOGICAL CONDITION ACTED ON BY THE TEST COMPOUND

GENERAL DISCUSSION

This field is for the entry of one of the following:

I (1) TEST ORGANISM ACTED ON BY THE TEST COMPOUND
(2) TUMOR ACTED ON BY THE TEST COMPOUND
(3) PATHOLOGICAL CONDITION OTHER THAN TUMOR ACTED ON BY THE TEST COMPOUND

II (4) TUMOR PRODUCED BY THE TEST COMPOUND

Organization

The Biology Code has been provided, as far as possible and to the extent of its anticipated needs, with unique symbols for the species of organism used or for the precise pathology treated. These symbols bear relationships to each other, based on relations between organisms or between diseases so that, first, retrieval of coded data is possible at any taxonomic level or at any level of pathology description and, secondly, appendage to the Code of new symbols for additional organisms or pathologies is possible in a logical relation to the pre-existing code items.

The symbols for organisms, pathologies, and tumors are assigned according to definite schemes. Since each scheme is specially designed to provide symbols which reveal relationships between organisms, or pathologies, or tumors, by any of their several characteristics, each can be considered essentially as a separate Code. The Taxonomy Code requires, for example, that a new organism be assigned a symbol whose first unit represents the phylum to which it belongs. As another example, the Tumor Code rules specify that, when a symbol is assigned to a new tumor, the second and third units of that symbol must represent the organ in which the tumor originated. Every organism, every tumor, and every pathology is coded according to the rules of that particular Code. However, once it is coded, it is added to the list of organisms, pathologies, or tumors so that it need never be coded again. These Field E lists, then, are actually groups of pre-coded items, any one of which will never vary in the coding of its identity. The lists of organisms, pathologies, and tumors are included in the CBCC Biology Code as the Taxonomy, Pathology, and Tumor Codes of Field E.

Following this general discussion of Field E is a separate discussion for each of the Taxonomy, Tumor, and Pathology Codes, explaining how the symbols are formed for organisms, tumors, and pathologies and what coded information about an organism, tumor, or pathology is incorporated into its symbols.

General Use

In Field E is coded the major biological component of the test data, the organism, the pathological condition, or tumor which is experimentally treated with the test compound. A pathological condition produced by the test compound (excepting tumors) is always identified specifically in Field T-2.

When a compound is tested for its ability to induce tumors, the effect tested for is coded in Field T (Field T-1, Symbol 7; Field T-2, Symbol 43: "induces neoplasm"). However, to provide for coded identification of any tumor actually induced, the tumor identity is coded in Field E and the organism in which it is induced is placed in Field J. Only in the case of tumor induction (Symbol 43 of Field T-2) is Field E used to code the identity of the result of the test compound's action. In all other cases, as explained above, an entry in Field E represents the organism, pathology, or tumor treated by the test compound.

It is important also that distinction between the uses and structures of symbols of Fields E and J be understood. Experience has proved that frequently the points of difference are not always

immediately appreciated and errors in coding result. All data for which the CBCC Biology Code is intended have at least two major components, (1) a biological organism or condition treated with--or a tumor produced by--(2) a test compound; a biological organism or condition treated (or a tumor induced) must be entered in Field E for every line of coded data. Field J, however, is coded only in the case of a pathological condition (coded in Field E) or when the test organism (coded in Field E) is growing in or maintained on a host. Field J, then, is for coding (1) the organism in which a pathological condition occurs or (2) the host organism or host substance in or on which a test organism is living. The symbols of one field are not in any way interchangeable with symbols of the other. Coding an organism in Field E, for example, must be by use of the Field E Taxonomy Code symbols and under no circumstances is by use of Field J symbols; Field J must never be coded with symbols from the Taxonomy Code of Field E.

Specific Directions and Explanations Related to Field E in General

1. Symbols which do not fill all eight columns of Field E; unused final columns of Field E are cross-hatched

In any of the Taxonomy, Tumor, or Pathology Codes, there are items represented by symbols of less than eight units. For example, if a test organism is only identified as to the family to which it belongs or if it were demonstrated that all members of the family respond to the test compound as the code line indicates, Field E would be coded with the symbol for the family. This would be a five-unit symbol, leaving Columns 23, 24, and 25 uncoded. As a second example, any non-specific, unnamed tumor would have a maximum of seven units, leaving Column 25 uncoded. The CBCC practice has been to cross-hatch any such final unused code boxes of Field E, since it thereby is assurance, when transferring the coding to IBM punched cards, that the final units are omitted intentionally and not because of an oversight or because a new symbol for a species or a named tumor is needed in the Code.

2. Symbols available for additional items of Field E

Since the IBM zone punches have not been given special meanings in Field E, any number or letter not already used in any of the IBM columns may be used to construct symbols for organisms, tumors, or pathologies.

3. File of coded biology data on IBM punched cards arranged according to symbols for organisms, tumors, and pathologies in Field E

The CBCC has maintained a complete file of IBM biology punched cards arranged by the Field E entries, referred to ordinarily as the "Taxonomy File". (Because the part of the Biology Code which has been entitled the "Taxonomy Code" is exclusively concerned with test organisms, this use of the "Taxonomy File" tends to be misleading. Possibly the file would better be referred to as the Test Organism-Tumor-Pathology file, since all of these are included in it.) Thus, to retrieve all information about any organism or group of organisms, or on any tumor or tumor type, or on any pathology, this file permits direct manual retrieval of the appropriate cards. The cards thereby obtained can then be sorted for any other specifically requested information coded in another field.

4. Double coding in Field E

IBM punching prohibits more than a single Field E entry on a single IBM punched card. Therefore, if two or more tests demonstrate that two or more organisms (or two or more tumors or pathologies) respond so nearly identically to a test compound that the only variation in the code line would be the entry in Field E, coding can not be abbreviated by constructing only one line with all the organisms (or tumors or pathologies) so responding coded in Field E. A line must be constructed for each organism, for each tumor, or for each pathology of such a situation.

FIELD E
Columns 18, 19, 20, 21,
22, 23, 24, and 25

Specific Directions and Explanations
Separately Outlined for the Use of Symbols for
Test Organisms, Tumors, and Pathologies in Field E

I. TEST ORGANISMS (Taxonomy Code)

1. Definition

By the term "test organism", reference is made to the organism against which the action of the test compound is directed, when this organism is not affected with a pathology or tumor which is itself being specifically treated. This term does not refer to any organism which is used in a test as the experimental host. (See Parts II and IV of this section for a discussion of tumor and pathology coding.)

2. Taxonomic categories below species are not distinguished by code in Field E

The code symbols for test organisms are exclusively in the Taxonomy Code of Field E. These symbols permit taxonomic distinction of phyla (or plant divisions), classes, orders, families, genera, and species, but not strains or varieties. Therefore, when all conditions are the same except that two or more varieties are used, lines can not be constructed for results on each variety, since the coding in Field E would only be identical for each variety in each line and the lines would appear to be mere repetitions or contradictions of each other. (An exception to this is permitted by use of Symbol F in Field G, only under conditions as described in Division 4 below. A second rare exception is made by the eighth unit of the symbol as explained in Division 5 below.)

3. Physiological strains may be indicated by code, but not in Field E

The preceding paragraph points out that the Code does not distinguish taxonomic categories below species. However, physiologically distinct strains of a species frequently occur and a general provision has been made for distinguishing certain of these by code. This provision consists of items in Field G (Symbols F; G, H, and I; 6 and J). Examination of these items of Field G will explain the extent of strain distinction possible. Field E by itself does not provide for strain distinctions any more than for taxonomic varieties.

4. Several taxonomic varieties or physiological strains tested by the identical test methods; coding procedure

In the case of data from tests on a number of taxonomic varieties or physiological strains, only a single code line should be constructed for all the organism forms showing a positive response, regardless of the degree, using the indiscriminate evaluation criterion, "Author's Evaluation", Symbol 01 in Field X, and the general evaluation, "Active", Symbol 0 in Field Y. If none of the varieties or strains of the series tested responded to the test compound (i.e., if the responses of all organisms were negative), the evaluation in Field Y would be "Inactive", Symbol 1. If only a few of the series of organism varieties or strains showed a negative response, code one line combining those showing a positive response; code a single line, combining those showing a negative response; test-organism-distinction between these two lines is made by coding, in the line for the negative responses, Symbol F in Field G. (See Field G, Specific Directions and Explanations, Division 9.)

5. Exceptional use, by the CBCC, of the eighth unit of the Taxonomy Code for indicating a variety or strain

Although the CBCC has largely adhered to the provisions explained in Divisions 2, 3, and 4 above, restricting the use of the eighth place of the Taxonomy Code symbols to designating species, an occasional exception has been allowed. When a particular taxonomic strain (e.g., cabbage: Brassica oleracea capitata) or a physiological strain (e.g., the DDT-resistant housefly) is so extensively used experimentally that (1) many lines of data will be coded for it and (2) there would be considerable advantage in being able to retrieve information on that strain by a single file sort, the strain is given a unique code symbol just as if it were a distinct species. If all information on the housefly, for example, is subsequently to be retrieved from a file of coded data, not only must the search be for

IBM punched cards with the symbol for the housefly otherwise undistinguished, but there must be included a search for cards with symbols of any and all housefly strains. Only by weighing the disadvantage of this additional complication in retrieval against the advantage of having the particular strain distinguished in Field E, has the CBCC made the decisions, which were special in each case, to permit certain strain distinctions by unique Field E taxonomy symbols.

6. Test organism versus host; distinctions

It is important that the coder understand the definition of a host organism, for which Field J is provided. In any experimental situation in which one organism is living as a parasite on another organism, there are three considerations to make, which will determine what will be coded in Field E:

(A) Was the compound being tested for, or did it produce, an action on the parasite and thereby affect the host? If so, the parasite should be coded in Field E and the host in Field J. (E. g., to code that the test compound causes some relief from malaria in chicks, the malarial organism is coded in Field E, the chick in Field J.)

(B) Was the compound being tested for, or did it produce, an action directly on the host, irrelevant to the parasite? If so, and that action is being coded, the host of this situation is actually the test organism to be coded in Field E and the infestation is merely an incidental condition which is indicated by coding Field G with Symbol 5. (E. g., to code that the test compound causes increased heart rate and 50% mortality in chicks with intestinal roundworms [or body lice or coccidia, e. g.] when the parasites in controls cause neither an altered heart rate nor death, the chicken is coded in Field E and Symbol 5 in Field G-1.)

(C) Was the test compound being tested for, or did it produce, an effect on some single symptom of the pathological condition of the host caused by the test organism, when the condition as a whole was not significantly affected? (This is a difficult coding problem; it is discussed later in this Section, in Part IV, Division 5.) The host of this particular situation is coded in Field J and the test organism (whose symbol in the Taxonomy Code is given synonomy, in the CBCC Pathology Code, with the pathology syndrome it causes) is coded in Field E; the action on the symptom is coded by the appropriate code symbols in Field T.

7. General directions

When coding of Field E is completed and this coding is not of a species but only of a genus or family so that one or more of the final code boxes in the field are left uncoded, those uncoded boxes are to be cross-hatched.

In the language portion, the complete scientific name of the organism is written and underlined. If the common name is given, it is also included, being written after the scientific name and not underlined.

II. TUMORS AGAINST WHICH COMPOUNDS ARE TESTED; TUMORS PRODUCED BY COMPOUNDS (Tumor Code)

1. Tumor against which a compound is tested

Any tumor, whether induced, transplanted, or spontaneous, that is treated with a test compound is coded in Field E by a symbol found in the Tumor Code of Field E. The animal, plant, or medium which harbors the tumor at the time of the test is coded in Field J as the host, whether or not that host is the parent source of the tumor. The parent source of the tumor, if different from the host in Field J and if not clearly implied by the tumor identity in Field E, can not be recorded by code, because providing a special coding field for this occurrence is impractical for the CBCC Code; however, this different parent source, under these conditions, must be recorded in the written abstract of Field E. For example, in coding data from a test with a mouse tumor transplanted to a culture medium, the medium would be coded in Field J, but the mouse origin can only be recorded in the written abstract.

If the location of the tumor is described as one specific organ of the host coded in Field J (i.e., any one specific item of Field H-1), that organ should be coded in Field H-1. This procedure satisfies the purpose of Field H-1 which is to record the responding organ.

If the tumor is a transplanted tumor, the one specific organ to which it is transplanted is coded in Field H-1, whether the organ of origin was of the host coded in Field J or of another organism. The CBCC Code considers the organ that is host to the transplanted tumor as being the diseased organ rather than the organ whose cells have altered to the tumorous state. Thus, if the organ of origin is different from the organ to which it is transplanted, the organ of origin is only recorded as part of the code symbol for the tumor. Whether the organ of origin is or is not indicated specifically by the tumor symbol in Field E, it should be included in the written abstract of Field E. Notice that there are being discussed here only transplanted tumors. For action on metastasizing of tumors, see Division 5 of the Specific Directions and Explanations of Field H-1 and the Code definition for Symbol 46 of Field T-2.

If the same tumor is described as being in more than a single organ (more than one specific item of Field H-1), it is ordinarily adequate to code only a single line with one of the organs coded in Field H-1. However, if the tumor response differs according to its anatomical location, as many code lines should be constructed as there are tumor locations that respond differently to a degree that can be distinguished by code in Field Y.

In the case of tumors being treated which are known to have been chemically induced, the fact that they were so induced is indicated by Symbol T ("chemically induced") in Field F; if the identity of that carcinogen is known, it may be included in the written abstract, but it is not considered a significant component of the data being coded and is not coded in Field D.

2. Tumors produced by compounds

Any tumor produced by a test compound is coded in Field E by symbols found in the Tumor Code of Field E. The organism in which the tumor is produced is coded in Field J, since it is the host of the tumor at the same time that it is the origin of the tumor.

If the location of the produced tumor is described as being in one specific organ, that organ should be coded in Field H-1; if the same tumor is produced in more than one organ, ordinarily only a single line is necessary, with one of the organs coded in Field H-1.

If a compound is tested as a carcinogen, yet no tumor is produced, Field E is coded merely with the Symbol S ("tumor, unspecified") in Column 18 and the organism treated with the candidate carcinogen is coded in Field J. This permits retrieving from the file all data on tumors, including negative carcinogenic data, by reference to a single field, Field E.

3. Coding distinction between tumors treated and tumors produced by the test compound

Although there is not a coded distinction, in Field E, between tumors which test compounds affect and tumors which test compounds produce, the coder will recognize that the two are distinguished by the coding in Fields T-2 and T-3.

4. Pretreatment of the host of a tumor

Any pretreatment given to the host or part of the host (including the anatomical site of a spontaneous or transplanted tumor), which results in a special experimental state of that host or structure, is coded only in Field L.

III. SOURCES OF ENZYMES ACTED UPON BY TEST COMPOUNDS

Enzymes are never coded in Field E; they are always coded in Field T-2. (See the Enzyme Code of Field T-2 and Division 22 of the Specific Directions and Explanations for Field T-2.) The animal or plant source of the enzyme is coded in Field E (Taxonomy Code) and, if the organ from which the enzyme is derived is known, that organ is coded in Field H-1. Frequently, in enzyme studies, Field G is coded with one of the Symbols U through X, to indicate the test preparation. (See the Code for definitions of Symbols U through X which will explain their use in this situation.)

In the case of enzymes described as purified, crystalline, recrystallized, etc., especially commercially available enzymes so designated, and undesignated as to biological source, code the source in Field E with Symbol Z, Z1, or Z2 and record all information given (commercial source, number of crystallizations, assay, chemical properties of the lot, etc.).

IV. PATHOLOGY TREATED BY THE TEST COMPOUND (Pathology Code)

1. Pathology treated vs. pathology produced; distinction in coding procedure

Only a pathological state that is treated by the test compound is coded in Field E, using symbols found in the Pathology Code of Field E. (The discussion of the Pathology Code will explain that a specific pathology is actually frequently represented by a basic pathology symbol in Field E combined with a specific code entry in Field H.) The production of a pathological state by a test compound is coded in Fields T-1, T-2, and T-3. (Consult Part V below for this latter situation.)

2. Host of the treated pathology

The organism that is in the treated pathological state is coded in Field J as the host of the pathology. (The pathological state is essentially coded in Fields E and H.)

3. Coexisting pathological conditions; only one is treated

If a complex of apparently unrelated pathological conditions exists in an organism and the test compound is administered to treat only one, the treated condition is coded in Field E and Field L is coded with Symbol 7 (or other appropriate symbol) to indicate that there are coexisting pathological conditions. (E.g., the test compound is administered to treat experimental hypertension in dogs which are incidentally anaemic and infected with mange.)

4. Coexisting pathological conditions; any or all treated

If a complex of apparently unrelated pathological conditions exists in an organism and the test compound is administered, with no clue as to which condition it was particularly intended to treat or with no intention of treating one more than the other, the policy is to code a line for each pathological state, recording either the negative or positive responses of each and indicating in each line (Field L) that coexisting pathological conditions exist. (E.g., the test compound is administered to a dog with pulmonary edema, conjunctivitis, and tapeworms; no improvement in any of the three conditions is observed.)

5. One pathological condition, several related conditions as symptoms

(See also Part I, Division 6, Subdivision [C].) When the situation involves a complex of related conditions (i.e., symptoms of a major pathology), the coding procedure must be based on the premise that it is desirable always to have coded in Fields E and H the major pathology, any or all of whose symptoms may be affected by the test compound. Therefore:

(A) When a test compound is administered to an organism with a specified pathological condition and only one of the symptoms of that condition responds but there is no evidence that any of the remaining symptoms respond, the specified major pathological condition is coded in Field E and the symptom that responded and its response are coded by appropriate symbols in Fields T-1 and T-2. If more than one, but not all such symptoms should respond, each symptom's response must be on a separate line in Field T-2.[1] The symptoms which did not respond to the treatment should not be coded on separate lines.

[1] In this particular situation, the CBCC policy has been to use discretion so that usually only one or two of a group of affected symptoms are actually selected for coding.

(B) When the specified major pathology is understood to be generally affected, either by all the symptoms being affected in the same way or by the author's specifically stating that one or more symptoms' responses are used merely as the author's basis for determining that the major pathology is generally affected, the major pathology is coded in Fields E and H, but the symptoms are not coded in Field T-2; instead, the general response of the major pathology is coded by one of the symbols of the 17-- or 16-- series in Field T-2 and there is recorded, in the written abstract portion of Field T-2, the evidence for that general effect on the major pathology.

(C) When two or more coexisting pathological conditions are treated by a test compound and they seem possibly related but there is no specific indication by the author that these are all symptoms of a single major pathology nor is the coder absolutely confident that these all represent a single major pathology, each condition must be coded in a separate line in Field E; i.e., each must be treated as a major pathology rather than the coder's attributing one to being a symptom of the other or, by conjecture, attributing both to a more general major pathology.

6. Pathological conditions caused by test organisms (infectious diseases)

The Pathology Code of Field E considers that each parasitic organism, by its own specificity, bears a unique relationship to its host and therefore causes a unique symptomatology, however small might be the distinctions in certain instances. On this assumption, any pathological condition caused by a specific organism can be defined most accurately by reference to that specific organism. Therefore, in the Pathology Code, there are a number of items referring to the pathological conditions caused by specific parasitic organisms and the symbol for each of these is merely the symbol for that parasitic organism in the Taxonomy Code of Field E. In other words, the symbol for each such infectious disease is exclusively etiological in nature, merely expressing the causative agent. The disease is made specific, when necessary, only by indicating in Field H in what organ or part the infectious disease is located.

V. TEST ORGANISM IN WHICH PATHOLOGY IS PRODUCED BY THE TEST COMPOUND (Field T; NOT the Pathology Code)

As pointed out in Division I of Part IV, above, when a pathological condition is produced by the test compound, the pathology is not coded in Field E, but it is coded by appropriate symbols in Fields T-1 and T-2, as the response to the test compound. The test organism in which this effect occurs is coded in Field E.

CODING OF TEST ORGANISMS

GENERAL DISCUSSION OF THE CBCC TAXONOMY CODE

1. Symbols for organisms; the taxonomic significance of parts of the symbols for organisms

Deriving the symbol for any specific test organism is itself a coding process. Once the taxonomic information about a given organism has been coded, the assembled coding represents, as a unit, the code symbol for the organism. The symbol remains constant for any given organism in the same way that symbols remain constant for organs in Field H or physical states of chemicals in Field A, etc. This coding of the taxonomic categories to which a specific organism belongs is dealt with here.

Field E provides eight IBM punched card columns for identifying the test organism. The total area of eight columns is divided into six sub-areas, each conveying unique taxonomic information. The eight units of the Taxonomy Code symbols (i.e., the eight IBM punched card columns of Field E) are apportioned as follows: 1, the animal phylum or plant division; 2, the class; 3, the order; 4 and 5, the family; 6 and 7, the genus; and 8, the species. This permits distinguishing 35 phyla; of each phylum, 35 classes can be distinguished; and, of each class, 35 orders can be distinguished. The two units for each of the family and genus designations permit distinguishing in each order hundreds of families and, in each family, hundreds of genera. The CBCC has elected to use as far as possible only numerical units for the familial and generic designations, (i.e., 01 through 99, rather than 01 through 0Z followed by 11 through 1Z and 21 through 2Z, etc.). This simplifies IBM punched card sorting, since letter designations, incorporated into the code symbols, can be indicated only by a combination of a zone punch and numerical punch and this double punch would require sorting the cards twice to retrieve any given letter designation.

Thus, when a coder uses a symbol for a specific organism, he is actually coding six pieces of pre-coded information, the identity of the phylum, class, order, family, and genus to which the organism species used in the test belongs.

2. Limitation of the number of species for which biological responses to chemicals are experimentally determined

In devising the Taxonomy Code, the primary objective was to satisfy the needs of the CBCC in the process of coding only the results of tests for biological responses. In other words, the ultimate objective of the CBCC Taxonomy Code was not the coding of all organisms; information about responses to chemicals may be expected for only a fraction of the total number of known species of organisms. While the CBCC has no reason to provide code symbols for all organisms nor necessarily for all organisms of any given group, its pattern for coding organisms has to permit coding taxonomic information about any given organism.

3. Essential taxonomic information about a test organism

In a coding project in which the information being coded involves only a few organisms, the identities of the organisms could conceivably be indicated very simply merely by assigning symbols in sequence. For example, a species of Aspergillus might be assigned symbol 1; a species of Clostridium, symbol 2; a species of Bacillus, symbol 3; a species of Amoeba, symbol 4; etc.

The needs of the CBCC for coded taxonomic information exceed any such simple scheme. It is necessary that the Center be able to associate all chemical-biological information related to all organisms of a given family, or of a given phylum, or of any other taxonomic category. Also, an organism is occasionally identified by the author only as a member of a broad taxonomic category, such as a member of a specific order or of a specific family, and the CBCC must be able to code in such a way that the code entry is clearly identified as a family or order and identified as to which family or order. Therefore, the scheme as described above in Division 1 was established, by which each organism species is coded to indicate the phylum, class, order, family, and genus to which it belongs.

This particular scheme also provides unique symbols for all the organisms for which symbols are apt to be needed in coding results of chemical-biological tests. (See Division 2, above.) While the CBCC Taxonomy Code does not pretend to be able to accommodate all known organisms (all species and all taxonomic categories) with the limited space of eight IBM punched card columns, the symbols available for each taxonomic category are actually in most cases more than sufficient to include all known members of the category. For example, 35 symbols of one IBM punched card column are ordinarily adequate to encompass all recognized phyla, or all classes of any one phylum, or all orders of any one class.

If a phylum is organized into more than 35 classes or a class into more than 35 orders, the CBCC Code could not conveniently provide symbols for all of them, but since it is not probable that chemical-biological data will be encountered for species from all of such a large number of classes of a single phylum (or of orders of a single class), or even from any but a part of 35 classes (or orders), a provision for more than 35 symbols has seemed, and has so far proved, unnecessary.

It will be noted that the coding scheme of the CBCC does not provide for distinguishing, by code, taxonomic intergroups (subgroups and supergroups), such as subclasses and superclasses. Any intergroup has the same symbol as the major group of which the intergroup is a member. For example, all of the suborders, Trichostomata, Gymnostomata, Astomata, etc., have the same code symbol (Symbol 121) as the order to which they belong (Holotricha). Therefore, it is not possible to use the symbol for an intergroup to sort out all information on only that single specific intergroup, since the symbol represents all intergroups of the major group (e.g., all suborders of a given order). The retrieval of information on all members of a suborder, for example, could be made by selecting coded information for all families known to be included in the suborder or by retrieving all information coded by the single symbol for the order and all its suborders, followed by inspection and manual selection for information on the suborder. While this complication appears to be a disadvantage, the actual improbability or infrequency of need for retrieval of information on an intergroup justifies omitting distinguishing code designations of sub- and supergroups.

4. The sequence of symbols in any one taxonomic category is only the sequence by which the names of taxonomic groups are added to the Code list

Generally, the taxonomic groups or species are added to the Code only when the need arises. Thus, to date, not only are a very limited number of species to be found included in the list, but, in most phyla, only a limited number of genera, families, orders, and classes. (Initially, an attempt was made to provide a basically complete list of phyla, classes, and in some phyla, orders.) When data are encountered involving an organism not yet in the CBCC list, the new symbol assigned to that organism consists of the seven-unit symbol indicating the phylum, class, order, family, and genus to which it belongs and a unique final unit which is simply the next sequential number or letter following that given to the last-added species of that genus. In the same way, if a genus is new to the list, the symbol given it consists of the five-unit symbol indicating the phylum, class, order, and family to which it belongs plus a new generic symbol (the sixth and seventh units of the total symbol) which is merely the next two-unit number or letter combination sequentially following that given to the last-added genus of that family. In a similar way, new families, orders, classes, and phyla are added to the list. Thus, within any single taxonomic category (e.g., an order), the symbols of its member groups (e.g., the families of an order) do not occur in a sequence that attempts to represent a natural phylogenetic relationship (i.e., more primitive families succeeded in the list by increasingly advanced families) nor is there any other organization such as an alphabetization of families within an order. Instead, the sequence of symbols for families within a single order represents merely the sequence in which they were added to the Taxonomy Code; the same is true for the sequence of symbols for the orders of a given class or genera of a given family, etc. The feature that permits any new member to be appended to the end of a list (rather than having to insert a new member into an organized list which would require altering the list to make it conform to the organization scheme) is sometimes referred to by the term "open-end". It will be noted that, in compiling the original lists, the phyla and, in many cases, the classes and orders, were placed in the list and given symbols in an order reflecting a natural taxonomic sequence, though no special significance is attached to it.

Inasmuch as natural relationships are as yet so little understood in many groups of organisms, natural classifications are in many cases still impossible; in some cases, much disagreement exists among students concerning taxonomy within a given group, for any of several reasons. Thus, no

contemporary attempt to establish a taxonomy code on a single existing taxonomic scheme can be expected to satisfy all persons nor posterity. Prior to publication, an effort has been made to review the organization of this Taxonomy Code, consulting what are believed to be authoritative sources of contemporary opinion. A number of revisions have been made which have resulted, in a few instances, in changed symbols for organisms already recorded at the CBCC. (When such a change in a code symbol is made, all IBM punched cards and code sheets on which the old symbol is punched or written must be recalled from the files and altered to conform with the new symbol.)

5. Indication of common names, synonyms, and intergroup names in the Taxonomy Code

Sources of chemical-biological data, whether published or unpublished, vary widely, not only in terms of investigators and geographic locations, but in temporal terms. Taxonomic identities, therefore, may vary accordingly, so that a name accepted at one time or by one person may be unacceptable at a later time or by another person, because of new information or because of differences in interpretation and opinion. Further, there are frequently encountered data in which identity of the organism is with only a common name. Names of intergroups (sub- and supergroups) are sometimes of importance, because a test organism may be identified only as to the intergroup of which it is a taxonomic member. Variations in classification permit one scheme to bestow full rank (e.g., order or class) on a group which another scheme considers as an intergroup (e.g., superorder or subclass, etc.). For the above reasons, there have been included certain of these names in this Code, for convenience in identification, as described in the following paragraphs.

When an intergroup is listed, the taxonomic groups included in that intergroup are defined to indicate their relationship, because the code symbols can not do this. For example, in the Pelecypoda (Mollusca), there are listed several suborders, for some of which several families are listed; the code symbols for the families can only indicate the order to which they belong, but, in each of these families' definitions, the suborder to which it belongs is indicated.

The question as to whether the groups considered here as suborders, for example, should instead be given the rank of orders and the orders given the rank of subclasses may often be academic or arbitrary, but proves vexing in composing code symbols because of sharp divergences of opinion among taxonomists. In making code symbols, however, some decision has had to be made in such cases, since the code symbols could not be constructed, according to the present method, to satisfy both or all of varying taxonomic opinions and organizations. This would suggest the difficulty attending any effort to invent a coding scheme for this category of information whose classification must shift with changing concepts of phylogenic relationships.

When it has been an advantage to do so, names are entered in the taxonomy lists to record slightly different taxonomic schemes. This has been attempted in some detail in the case of the phylum Chordata and the fishes and occasionally in other groups. For example, in the list of Protozoa, the name Rhizopoda is listed twice, once as a synonym of Sarcodina, being considered as a class; however, Rhizopoda appears in other schemes as a subclass of Sarcodina and is listed a second time to indicate this. Subsequently, the family Vampyrellidae is listed as belonging to either of two orders, according to the taxonomic scheme preferred, Amoebozoa (order of class Sarcodina) or Proteomyxa (order of subclass Rhizopoda).

Certain synonymous names are included in the list. These synonyms for a given group or a given species are assigned the identical code symbol. The synonymous names might all have been listed together (in series) as a single entry; they are listed separately because, when scanning the list, a name is not easily found if it is not aligned with all other names in the list.

In some instances, a name has been included which is for a group (e.g., an order) that the CBCC Code has considered as two or more separate groups (e.g., two or more orders). In this case, the name is included in the list essentially for reference purposes only; the symbols listed with the name are not to be used as such for coding, except that, if an author should express the chemical action as being generally on all organisms of this composite group, it must be assumed that organisms of each group recognized by the CBCC code as separate groups are affected as described and, to code this completely, a code line for each group would be necessary. For example, the Coelenterate order Hydrocorallina is listed, but only with both Symbols 313 and 314, indicating that this term is not

recognized except historically by the CBCC code as having once been described to encompass organisms of the recognized order Milleporina (Symbol 313) as well as organisms of the order Stylasterina (Symbol 314). If an organism is identified only as to such a composite taxonomic group of which it is a member, it is usually advisable to code a single line, with the organism coded only to the category above the composite category (e.g., to the family of a composite genus with which the test organism has been identified).

Where there are included in the list names for groups which the CBCC Code recognizes as being incorporated into a single group (e.g., two or more orders being recognized by this list as a single order), the symbol for each of the smaller groups is identical to that for the single CBCC-recognized group. Accompanying each such name in the list is the explanation that it is considered as being included in another, specified, single group. For example, classes Chondrichthyes and Osteichthyes are both considered as being incorporated into the single class Gnathostomata, Symbol A, and therefore are both assigned Symbol A, with an explanation with each that they are represented by the composite class Gnathostomata. If a chemical response is described as generally typical of all organisms of a group which the CBCC Code recognizes as being incorporated into a group of another name, the coding is unable to distinguish the restriction of the response to the group described by the author and it is important that, besides writing the name of the group which the author describes, there be included in the written abstract the notation that the group is incorporated into the composite group which is represented by the CBCC symbol used.

Names for sub- and supergroups are incorporated into the list as part of the taxonomic schemes, although they cannot be distinigushed by code. Refer to Division 3.

Common names are given a symbol identical to that for the scientific name of the species or group.

In no case is there pretended a completeness in the listing of common names, intergroups, or synonyms.

6. Adaptation of the CBCC Taxonomy Code

The foregoing discussion has emphasized that the CBCC Taxonomy Code has been designed with the specific needs of the CBCC in mind. This approach in explanation has been made at the risk of creating an impression that the Taxonomy Code is in some way highly specialized and of little use other than for coding of chemical-biological information. That this is not true will be understood by even casual reflection. The Center has assumed that its Taxonomy Code represents a pattern of organization that could be used for virtually any project coding biological information when it is desirable to identify organisms by code. Since it has proved satisfactory for the CBCC, it is believed to be adequate for most purposes precisely in the form presented here. On the other hand, the pattern might be used, but simplified or expanded, according to special needs.

7. Other systems for coding organism identities

Time has not permitted compiling a bibliography of taxonomic codification systems. When the CBCC organized its Taxonomy Code, there was nothing on which the CBCC might have patterned its code to suit its needs and there was therefore no recourse but to develop its own system. A system used by the Entomology Department of the State Plant Board of Florida and the Statistical Laboratory of the University of Florida, Gainesville, Florida, has been described in an article published in 1958[1]. This system is very similar to that used in making the CBCC Taxonomy Symbols; the essential difference is that of restricting symbols entirely to numerical units rather than using IBM zone punches to provide letter units. Thus, having available only nine numerical punching positions in each IBM punched card column, two columns have been used to provide 99 available symbols or three columns for 999 available symbols. The two systems are compared by the following opposing lists.

[1] Taxonomic Codification of Biological Entities by H. A. Denmark, H. V. Weems, Jr., and Carlis Taylor; Science, Vol. 128, No. 3330, Oct. 24, 1958, pages 990-992.

	Number of IBM punched card columns used and (parenthetically) the number of symbols made available thereby	
Taxonomic Category	CBCC	ED, SPBF, and SL, UF, Gainesville
Kingdom	(Not Coded)	1 (9)
Phylum	1 (35)	2 (99)
Class	1 (35)	2 (99)
Order	1 (35)	2 (99)
Family	2 (1225), potential[1]	3 (999)
Genus	2 (1225), potential[1]	3 (999)
Species	1 (35)	3 (999)

[1]The CBCC prefers to use only numerical symbols for families and genera (though for phyla, classes, orders, and species, both numerical and letter symbols are used). Thus, in practice, the CBCC Taxonomy Code accommodates only 99 families of each order and 99 genera of each family; however, if it proved necessary, letter symbols could be used for families and genera after numerical combinations were exhausted, to provide symbols for up to 1225 families and 1225 genera.

8. References and acknowledgments. (Reference numbers in this division refer to a bibliographic listing at the end of the division.)

In reviewing the CBCC Taxonomy Code and making revisions when they seemed appropriate, various sources were consulted for the preferred taxonomic schemes on which to base the code symbols. In certain groups, it has seemed advisable, for this publication, to alter the scheme of code symbols from that set up earlier and used for CBCC coding.

The Protozoa, Porifera, Cnidaria, Platyhelminthes, Acanthocephala, and Echinodermata have been somewhat revised, largely in accordance with opinion expressed in the volumes issued to date of The Invertebrates by Dr. Libbie H. Hyman[1]. The classification of the Digenea (Platyhelminthes, Trematoda)--that on which is based the scheme of code symbols--now follows closely that of Dr. George LaRue[2], who was most kind in checking the Trematode list. For purposes of the present Code, this scheme was projected by the CBCC to cover all Trematoda. The Cestoda and Turbellaria arrangements are based largely on the schemes described in The Invertebrata, Volume III[1]. In revising the list and code symbols of Nematoda, Mrs. May Belle Chitwood of the Parasite Station at the USDA Experiment Station, Beltsville, Maryland, has given valuable advice.

For the Annelida, a number of references conveniently at hand were consulted, including organizations indicated in Fresh-Water Invertebrates of the United States by T. W. Pennak[3] and The Oligochaeta by J. Stephenson[4], although older ("obsolete") names appearing in the list, included for reference purposes, are derived from certain older texts. However, the scheme on which are based the code symbols is the result of advice from Dr. Libbie Hyman (American Museum of Natural History, New York, N. Y.) and Dr. Marion Pettibone (University of New Hampshire).

Other taxonomic groups, after being checked as far as possible at the CBCC, were submitted during 1957 to authorities of the U. S. National Museum for review and criticism and for assistance in filling in certain omissions. For the generosity of advice and time given by these persons, the CBCC is most grateful.

Mollusca	Dr. Harold A. Rehder
Crustacea	Dr. Fenner A. Chase, Jr.
Insecta	Dr. J. F. Gates Clarke
Fishes	Dr. Ernest A. Lachner
Amphibia and Reptilia	Dr. Doris M. Cochran
Birds	Dr. Herbert G. Deignan
Mammalia	Dr. David H. Johnson

FIELD E; Taxonomy Code
Columns 18, 19, 20, 21,
22, 23, 24, and 25

The publication prepared for the AAAS, Zoological Names, A List of Phyla, Classes, and Orders, edited by A. S. Pearse, Fourth Edition (1949) has been invaluable as a guide against which to check the taxonomic organization set up earlier by the CBCC and for preparation of revised lists prior to requesting final checks by the authorities listed above.

The bacteria and virus sections of the Taxonomy Code have caused particular concern due to extensive revision of the sixth edition (1948) of Bergey's Manual of Determinative Bacteriology[5], upon which the CBCC bacteria and virus code lists were patterned. The present list represents a compilation in accordance with the new (1957) Manual, made during the time the Manual was being prepared for publication. This would not have been possible without the help of Dr. R. E. Buchanan of Iowa State College through whose kindness the CBCC was given the use of a secretarial galley proof of the seventh edition and who also checked the final list composed for the CBCC Taxonomy Code for accuracy in accordance with later editorial changes. Lieutenant Erwin F. Lessel, Jr., of Walter Reed Army Medical Center, contributed considerable assistance in checking the validity of many genera and species of bacteria and viruses.

The virus nomenclature retains the pattern of the sixth edition (1948) of the Manual of Determinative Bacteriology upon the advice of Dr. F. O. Holmes of the Rockefeller Institute for Medical Research.

The American Type Culture Collection's list of bacteriophage strains was followed in listing the phages.

In checking the list of plants in the Taxonomy Code, the following botanical reference books were used: A Dictionary of the Fungi by G. C. Ainsworth and G. R. Bisby (Second Edition, 1945); Genera Siphonogamarum by C. G. DeDalla Torre and H. Harms; Cryptogamic Botany, Vol. I, Algae and Fungi by G. M. Smith (1938); The Algae and Their Life Relations by J. E. Tilden (1935); and Cryptogamic Botany, Vol. II, Bryophytes and Pteridophytes by G. M. Smith (1938). The list of Fungi were checked by John E. Stevenson, U. S. Department of Agriculture, Plant Research Station, Beltsville, Maryland.

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[1] The Invertebrates by Libbie Henrietta Hyman, four volumes; McGraw-Hill Book Co., Inc.: Protozoa through Ctenophora, Vol. 1, 1940; Platyhelminthes and Rhynchocoela, Vol. II, 1951; Acanthocephala, Aschelminthes, and Entoprocta, Vol. III, 1951; and Echinodermata, Vol. IV, 1955.

[2] The Classification of Digenetic Trematodes: A Review and a New System; by George R. LaRue; Experimental Parasitology 6 (3), May 1957, 306-349.

[3] Fresh-Water Invertebrates of the United States by R. W. Pennak; The Ronald Press Co., N. Y., 1953.

[4] The Oligochaeta by John Stephenson; Oxford University Press, N. Y., 1930.

[5] Bergey's Manual of Determinative Bacteriology, Seventh Edition by R. S. Breed, E. G. D. Murray, N. R. Smith, et al; The Williams and Wilkins Company, 1957.

CODING OF TUMORS

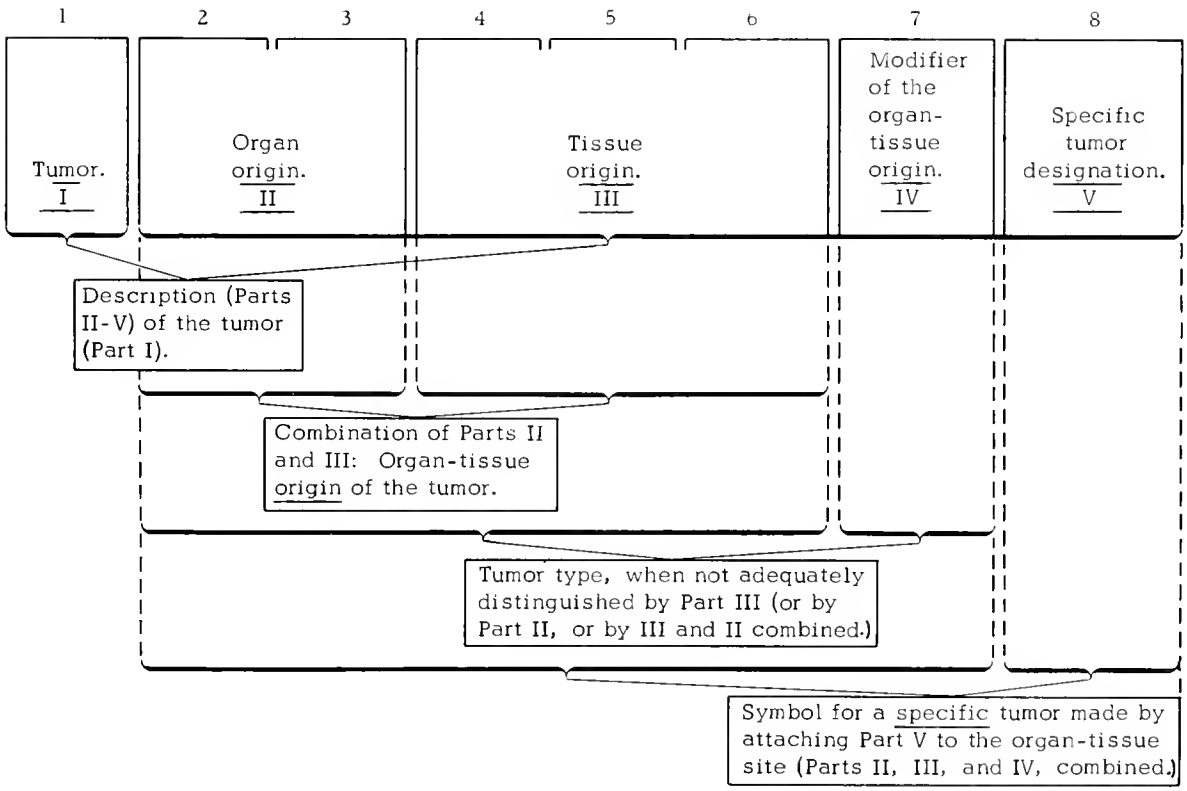
GENERAL DISCUSSION OF THE CBCC TUMOR CODE

1. Information about a specific tumor

Tumor symbols are derived by a coding pattern different from that for other pathologies. The list of tumors, with the symbols which represent coded information identifying the tumors, is therefore a separate and distinct list and is designated as the CBCC Tumor Code.

This description of the Tumor Code is essentially concerned with the pattern for coding, within Field E, information about the tumors themselves. The coding of information about a given tumor results in a combination of symbols in IBM Columns 18-25, which collectively represent the total, fixed symbol for the tumor. The section of the Key giving specific directions for using in Field E that prepared symbol for a tumor, when coding information about chemical tests, is included in the preceding General Discussion of Field E.

In coding identifying information about tumors, Field E is divided into five sub-areas for five specific categories of information about each tumor, just as, in the case of the Taxonomy Code, Field E is divided into six sub-areas for description of phylum, class, order, family, genus, and species. The diagram below illustrates, for tumor coding, the distribution of the eight IBM punched card columns (1-8, in the diagram) among the five sub-areas of Field E (I-V) and indicates the category of tumor information coded in each sub-area. The paragraphs that follow explain in turn each of the five parts. For consistency, the five sub-areas are referred to hereafter as "parts" of the total 8-"unit" tumor symbol.



Each Field E symbol for a specific tumor is the result of a tumor coding procedure described by the diagram of the previous page and the following paragraphs, just as a total code line of chemical-biological data is the result of a coding procedure using all coding fields. (See also the second paragraph of the section on Organization, in the General Discussion of Field E.) Any tumor not previously coded by the CBCC is coded by the procedure described below and is added to the tumor list in the Code. Therefore, when coding chemical-biological data involving that tumor, its symbol is quickly available, not only sparing coders from repeatedly having to code the tumor (i. e. , prepare the code symbol), but assuring uniformity when coding chemical-biological information on that specific tumor.

2. Part I of the tumor symbol (first unit, Column 18): identification of the symbol as a tumor symbol

Of the eight places in the tumor symbol (for the eight columns of Field E), the first is used merely to distinguish all tumor symbols from any other entry in Field E (i. e. , from symbols for test organisms and for non-infective diseases). Thus, by retrieving from a file of coded data all Field E entries with this first unit (Symbol S) which is common to all tumor symbols, all information on tumors, but only on tumors, can be obtained. Since tumors are coded in the same field in which organisms as well as pathologies are coded when appropriate, this first identifying part is essential. However, it might be pointed out that, were tumors to be given a separate coding field (impractical as far as CBCC coding facilities are concerned) or if only tumor data were coded, Part I would be unnecessary.

As the diagram indicates, the remaining four parts of the Tumor symbol describe and identify the tumor.

3. Part II of the tumor symbol (2nd and 3rd units, Columns 19 and 20): gross anatomical tumor origin (organ or system)

This independent, two-unit part of the symbol signifies the organ or organ system from which the tumor originated and it is referable to a separate code scheme for these organs or organ systems. Unlike the anatomy part of symbols of the CBCC Pathology Code, these anatomical symbols included in the Tumor Code symbol are not to be found in the code list of anatomical items for Fields H-1 and H-2, but only in the special list included in the Code accompanying the list of tumors. This special anatomy code consists of a first unit, indicating the system of which the organ is a part, and a second unit, which is merely a sequential number assigned to each organ of that system.

For the most part, organs (and tissues) of one chordate animal group are homologous to the organs (and tissues) of any other chordate group so that the same symbols are applicable to all Chordata. Organs and tissues of invertebrates (insects, e. g.) are scarcely homologous to chordate organs and tissues, but these may be inserted in the list as specific invertebrate organ or invertebrate tissue items under the appropriate organ or tissue system of the list. Since so few invertebrate tumors may be expected to be chemically treated, experimentally, it is consequently expected that all such symbols needed (for invertebrate organ and tissue tumor origins) can be adequately accommodated by available symbol combinations.

Thus, complete tumor symbols do not have any specific unit which indicates from which animal or animal taxonomic group the tumor originated. However, since tumors are seldom if ever transplanted to an animal of a phylum or class different from that of the tumor's origin, the phylum or class of the animal from which the tumor arose will be indicated in Field J (the tumor host). Rare exceptions to this occur in tissue culture studies (e. g. , a mouse tumor explanted to a chick embryo), in which case the animal in which the tumor originated is merely recorded in the written portion of Field E. See also the General Discussion of Field E, Division 1 of the special section on Specific Directions and Explanations for Tumors.

If the CBCC Code were adopted for recording data from tumor tests especially or exclusively, a new field might be established for recording the specific organism in which the tumor originated, if different from the host coded in Field J. For example, such a field would be desirable if data were being recorded from tests dealing solely with attempts to establish tumors of one species or genus in another species or genus. Since the CBCC Code is designed exclusively for testing chemicals (as carcinogens or carcinostats, e. g.), there is little anticipated need for identifying the organism in

which a tumor originated to provide for the relatively few occasions when it is different from the organism coded in Field J. The CBCC assumes that the organism in which the tumor is grown at the time of the chemical test has been demonstrated to be a satisfactory one, else it should not have been used for the test; assuming this, the information about the species origin of the tumor, when different from the organism in Field J, occurs too infrequently to justify reserving coding space on the IBM punched card for it.

Plant structures are so different from animal structures that a separate group of organ symbols is provided for them in constructing tumor symbols, since data on chemical treatment of plant galls (tumors) do occur. These symbols for plant structures are all assigned Symbol S as a first unit, with the second and third units (Part II of the symbol) representing the specific structure. For example, SS6----- is a tumor (gall) of a plant leaf.

The coding of the anatomical origin of specific tumors, indicated by units two and three of the tumor symbol, does not duplicate entries in Field H-1. In the case of tumor test data, coding the site of the tumor in Field H-1 is restricted to recording the site at the time of treatment. If the tumor is a spontaneous tumor and is treated by a test compound in the identical organ from which it arose, the anatomical coding in Field E (units two and three of the tumor symbol) and the anatomical coding in Field H-1 are duplications in essence if not by definition; this would also be true if the tumor were transplanted, but to the same organ of another individual (e. g., a mouse mammary carcinoma transplanted to the mammary gland of another mouse of the same species or strain). However, many chemical-biological test data concern experimental techniques using a standard tumor transplanted to sites other than the organ or body part from which the tumor was derived. The organ of origin is indicated by the tumor symbol in Field E; the transplantation site is coded in Field H-1. Retrieval of information (from a file of coded data) on tumors with given specific organ origins will be by sorting in Field E, while retrieval of information on tumors in given specific organ locations (whether originating in those organs or not) will be by sorting in Field H-1.

Since the next part of the tumor symbol (units four through six, described in the next paragraph) occasionally implies the tumor's anatomical classification, the use of the second and third units (for anatomical association) may sometimes appear redundant. Indeed, in the case of occasional tumor symbols, considered individually, this redundancy is a fact. (For example, S3412301 is a symbol for a urinary bladder tumor of transitional epithelium. Since transitional epithelium is almost restricted to the urinary bladder and associated structures, Part II [-34-----] is near redundancy to Part III [---123--].) However, it will be noted that essentially standard tumor classification is based on general tissue types rather than on specific organs in which they have originated and it is on this organization by tissue types that units 4, 5, and 6 are correspondingly organized. Since, in a general way, organs and organ systems are constructed of more than a single tissue, an organ or organ system may given rise to tumors of not only one, but frequently more than one tissue type. Connective tissue tumors, in particular, serve to illustrate this, since such a tumor would be classified with all other connective tissue tumors, regardless of the organ in which it specifically arose. Therefore, a code symbol, which indicated only that it was a connective tissue tumor and did NOT indicate that it was of a specific organ, would not permit that tumor's organ-relation (i. e., association with any and all other tumors of that specific organ) being indicated by code. However, by providing the units for specifying the organ or organ system, when a tumor is specifically associated with (i. e., has arisen from) an organ or organ system, it is possible to retrieve, from a file of coded data, information on all tumors of any given organ or system by a single mechanical sort (e. g., information on all tumors of the mammary gland, regardless of their being adenocarcinomas [epithelial], fibrosarcomas [connective tissue], melanomas, or otherwise).

4. Part III of the tumor symbol (4th, 5th, and 6th units, Columns 21, 22, and 23): tissue origin

The fourth, fifth, and sixth units of the tumor symbol are organized to parallel standard tumor classification and nomenclature, which is essentially based on tissue types. The fourth unit of the tumor symbol (i. e., the first unit of Part III) indicates to which large general histological group the tumor belongs. Thus, symbols for this fourth unit have the following definitions.

Symbol for the fourth unit (Column 21)

Animal tumors

1 Epithelial tumors (including all tumors derived from glandular tissue, regardless of its being endocrine or exocrine gland tissue)
2 Hemopoietic tumors: tumors of blood and lymph and blood- and lymph-forming tissues
3 Connective tissue tumors
4 Miscellaneous tumor tissue types difficult to identify with normal tissues: "round cell tumors", "spindle cell tumors", etc.
5 Muscle tissue tumors
6 Vascular tissue tumors; endothelial tumors
7 Nerve tissue tumors and tumors of tissues of the nerve sheath, meninges, etc.
8 Pigment tissue: melanin-forming-tissue tumors (often related to, or are of, nerve tissue origins)
9 Tumors of mixed tissues including teratomas
A Embryonic tissue tumors

Plant tumors

J Epidermal tissue tumors (plant)
K Vascular tissue tumors (plant)
L Parenchymal tissue tumors (plant)
M Pigment tissue tumors (plant)
N Embryonic tissue and mixed tissue tumors (plant)

The tumors included in this published edition of the CBCC Biology Code are listed according to their tissue origins. Therefore, that list itself includes, in consecutive sequence, the definitions of the above symbols for major tissue types. In addition, by virtue of this arrangement of the tumors, the definitions for symbols of units five and six (see the following paragraphs) are likewise evident in the Tumor Code list. This makes unnecessary a special listing of the tissues and their symbols, either here or in the Code, beyond the introductory outline above.

The fifth unit represents a subdivision of the major tissue type of tumor. For example, when Symbol 1 (tumors of epithelial tissue) is the fourth unit, Symbol 1 as the fifth unit signifies a tumor of glandular epithelium, while Symbol 2 in the fifth place indicates a tumor of non-glandular epithelium.

In the same way, the sixth unit represents a subdivision of the tissue type indicated by the fifth. For example, Symbol S--111 represents tumors of endocrine glandular epithelium, whereas S--112 represents tumors of exocrine glandular epithelium.

Although the organ-designating part of the tumor symbol (the second and third units) and the tissue-designating part (the fourth, fifth, and sixth units) have independent meanings, it is the combination of the two parts in any given tumor symbol that serves to identify exactly the place of origin of the tumor. Therefore, these five units (2-6), considered in combination, make up a single location-identifying unit, designating the origin of the tumor represented by the symbol. (See the diagram included in Division 1 of this description of the Tumor Code.)

5. Part IV of the tumor symbol (seventh unit, Column 24): modifier for distinguishing tumors of identical organ-tissue origins (Parts II and III); causative agents of plant galls

Since, in general, tumors have been regarded as being characterized by the tissues from which they arose and have been named to reflect this, the tissue designation of Part III (units 4, 5, and 6 of the tumor symbol) is frequently adequate for distinguishing a tumor type, or Part III and Part II (the organ origin), as a combination, is adequate. This is not always the case, however, and it is frequently important to be able to distinguish two or more types of tumor which are not distinguished merely by coding the organ and tissue origin.

Part IV (unit seven of the tumor symbol) is used for the final distinction of any tumor type, whenever preceding units of the symbol have been inadequate. It is used very loosely and without a strict definition, since it is thereby more useful from the standpoint of providing unique symbols.

Examples will explain best the use of the seventh unit:

A. Tumors of glandular epithelium, unspecified (i.e., when the type of gland is not specified, nor is the glandular organ specified, Symbol S0011---) have been distinguished as unspecified adenocarcinoma, unspecified adenoma, and unspecified papilloma by using the seventh unit: S001101-, S001102-, and S001103-, respectively. This does not mean that it is intended that all adenocarcinomas are designated by Symbol 1 as the seventh unit, nor all papillomas by Symbol 3 as the seventh unit. (Pulmonary adenocarcinoma C4461, e.g., is S2111221, Pulmonary Carcinoma MT8 is S2111231.) Instead, it serves in this particular case to modify the specific symbol, S0011--- (i.e., distinguishing three types of tumors described by the specific symbol, S0011).

B. Consider the epithelial tissue tumors of the lung. Here the seventh unit has been used to distinguish pulmonary adenomatosis (S211121-), pulmonary adenocarcinoma (S211122-), pulmonary carcinoma (S211123-), and pulmonary adenoma (S211124-). It does not mean that all adenocarcinomas are designated by Symbol 2 as the seventh unit (though all pulmonary adenocarcinomas are distinguished by it) nor all carcinomas by Symbol 3 as the seventh unit, etc.

C. Note the two symbols, S5A1111 and S5A1112, both of which represent endocrine gland tumors (---111--) of the ovary (-5A-----). It happens that the ovary contains more than one tissue that is described as endocrine and tumors may arise from each. Thus, the seventh unit is used to distinguish ovarian endocrine granulosa cell tumors (S5A1111-) and ovarian endocrine luteomas (S5A1112-).

D. The seventh unit has been used to distinguish any aleukemic form of leukemia (S--21-2-) from the more common type in which there is a great increase in blood leukocyte numbers (S--21-1-).

The seventh unit has an additional use, peculiar to plant tumor symbols, in distinguishing galls relative to their causative agents, such as microorganisms, insects, or chemicals. This factor of the causative agent has perhaps more significance relative to classification of galls than it has relative to classification of animal tumors and therefore one unit, the seventh, has been allotted this coding function in making symbols for galls. For example, Symbol SS6N001- is interpreted as: a chemically-induced (------1-) tumor (S-------) of mixed tissues (---N00--) of a plant leaf (-S6-----). In coding such a plant tumor, the specific causative agent (in the example above, a specific gall-producing compound) must be included in the written abstract portion of Field E.

In the case of animal tumors, the seventh unit has no special meaning or significance other than as a modifier. In other words, it is not reserved for especially indicating, for example, malignancy, tumor form, special tissue, nor special organ, though it may modify and provide specificity of the organ-tissue origin on the basis of any of these. For this reason, an arrangement of the Tumor Code items in a sequence according to Part IV (the seventh unit) would be meaningless (except that for plant galls the arrangement would be by causative agents).

6. Part V of the tumor symbol (eighth unit, Column 25): designation for specific, named, and transmissible tumors

The eighth unit provides a final, distinguishing part for specific, named tumors. For example, there are included several specific ovarian granulosa cell tumors, all with units 1-7 being S5A1111-; the symbol for each of these specific tumors is completed by assigning a final, eighth, sequential unit determined merely by the arbitrary way of its being listed or added to the list. Thus, ovarian granulosa cell tumors 18C57, 0L, and E4478 are given the following unique CBCC code symbols: S5A11111, S5A11112, and S5A11113. A non-specific ovarian granulosa cell tumor would be coded by Symbol S5A1111 (no eighth unit). In the case of plant galls, there are anticipated but few symbols with an eighth unit indicating a specific gall, since individual galls are seldom named and maintained as specific tumors, in the way certain experimental animal tumors are. In plant tumor symbols, nevertheless, the eighth unit is left open for any that might be so individually named and maintained.

For any given tumor type (indicated by units 1 through 7 of the tumor symbol), there may be several or many specific tumors which must be distinguished by unique symbols in the eighth place. Symbols 1 through 9 and A through Z in the eighth place permit unique code symbols for 35 specific tumors. In most cases, this is more than adequate provision. If more than 35 occur, however, and must be assigned symbols, they can be accommodated only by the procedure as described in the division immediately following.

7. Construction of symbols for specific tumors of identical organ-tissue origins, when more than 35 such tumors must be included in the Tumor Code

When there are more than 35 specific tumors with identical organ and tissue-type origins, the SEVENTH unit, coding that tissue type, may be combined (on the IBM punched card) with a zone punch (which will make it a corresponding letter designation) and the sequential numbering of the EIGHTH place repeated for the next thirty-five tumors of that tissue-type. In the present tumor list, this occurs only once, in the case of mammary gland adenocarcinomas. After the 35th adenocarcinoma was listed (Symbol S911121Z), the 12 zone punch was added to the seventh unit (Symbol 1), which converted it to the corresponding letter (Symbol A) and sequential numbering and lettering was begun again in the eighth place; thus, the symbol for the 36th adenocarcinoma is S91112A1. In this example, by using both the 11 and 12 zone punches for combinations, it is possible to accommodate 105 mammary adenocarcinomas in the list. (It happens that Symbol 1 can not be meaningfully combined with the IBM 0 zone punch, though other numerical symbols, 2-9, can; see the following paragraphs.) By this means, information on all mammary adenocarcinomas can be retrieved from a file of coded data by sorting solely on the Symbol S911121, ignoring the zone punches, while information on any given mammary adenocarcinoma can be found by sorting on its specific symbol, including any zone punch designation. (In this example, it should be noted that the letter designations formed by using the zone punches [letters A and J, formed by combining Symbol 1 with the two zone punches in turn] can not subsequently be used again as distinguishing seventh units for symbols for tumors of the type coded by the six-unit symbol, S91112--. For this reason, only numerical symbols 1 through 9 are used as a seventh unit [except as a continuation, as just described] in listing specific tumors of a given organ-tissue type.)

In the case of the seventh unit being any numerical symbol other than 1 (and 0, discussed in the next paragraph), that symbol can be combined with the 0 zone punch as well as with the 11 or 12 zone punches so that 140 specific tumors of a given organ-tissue source are possible in the list. (E.g., combining Symbol 2 with all zone punches in turn makes possible a set of 35 tumors for each of the four symbols, 2, B, K, and S, as the seventh unit.)

When a symbol for any particular organ-tissue type of tumor (units one through seven) has less than seven units (e.g., glandular tumors of the fundic stomach, S1A112--) and is incorporated into a specific tumor symbol, Symbol 0 is used as a unit or units between the final unit of the tumor-type code designation and the eighth unit; for example, Carcinoma 303, S1A11201. (This is explained again, in a slightly different way, in Division 8, below.) Thus, in the case of any specific named tumor, of a tumor type whose symbol is less than seven units, the seventh unit of the eight-unit total symbol is always 0; this seventh unit symbol, 0, can be combined with eighth units in only 35 ways for 35 specific tumors. This is due to the fact that numerical Symbol 0 (= zone punch 0) can not be combined on the IBM punched card with the other numerical symbols (2-9) to make corresponding letter symbols, because this combination is reserved for those other numerical symbols when they occur as seventh units. (Refer to the first paragraph of this division.) However, it is suggested that, in enlarging the Tumor Code, if there actually occurs a series of more than 35 specific tumors with identical organ-tissue origins and with their seventh units being Symbol 0, it will be possible to combine the 0 with one of the other zone punches (written on the code sheet as $\overset{*}{0}$ or $\overset{\#}{0}$) to make 70 combinations for 70 more specific tumors.

Even though specific tumor symbols may have Symbol 0 as their seventh unit (or as any or all of their second to seventh units), or though specific tumor symbols may have letter symbols as their seventh units, neither Symbol 0 nor any letter symbol in the seventh place can be interpreted as representing that tumor type. When searching information files for all data on tumors of a given type, therefore, the tumor list should be consulted for the symbol for that particular tumor type; that symbol will not end in 0 nor, if it has seven units, will its seventh unit be any symbol other than numerical, 1 through 9.

8. Use of Symbol 0 as a unit or units in constructing tumor symbols

When any specific, named tumor on this list (i. e., a tumor demanding an eighth unit in its symbol) is of such a general nature that there is no relation to a specific organ or organ system origin (i. e., the second and third units of the tumor symbol), the third--or the second and third--units are assigned Symbols 0 or 00, respectively. In the same way, if any specific tumor of the list is classified histologically (i. e., the fourth to the sixth units) so that less than three units are needed, the sixth, or both the fifth and sixth, or all three places are assigned Symbol 0 (i. e., 0, 00, or 000, respectively).

A specific and named tumor for which no histological or organic information exists may be added to the Tumor Code and assigned a symbol with any or all of the second through the seventh units being Symbol 0 and with a distinguishing symbol as the eighth unit, so that this specific tumor will have a symbol with the full complement of eight units, indicating a distinct and specific tumor. Example: Sarcoma M4 (S0040001). (Notice that in coding tumor data in which the tumor is not named as a specific, unique, transmissible tumor, that tumor is not added to the Tumor Code and no specific symbol is assigned to it. It is coded merely as being a tumor, Symbol S, in the first column of Field E, with the other seven places blank, or as a tumor of a specific organ [the first three places only, of Field E], or as a tumor of a specific tissue type [the first and the fourth places only], etc.)

9. CBCC Tumor Code: an initial and representative list; responsibility in making permanent additions

Although this is a more extensive listing of tumors than would be represented by those for which the CBCC has actually found test data, it does not, on the other hand, pretend to be an exhaustive list of known, named tumors nor of tumor types. New tumors, however, can be added to the list and symbols can be constructed for them in the same way as tumors have been added in the past.

It should be understood that construction of new symbols for the Tumor Code (or, for that matter, for the Pathology Code or the Taxonomy Code of Field E), is itself a coding procedure. The symbol that is assigned to any given specific tumor must have correctly incorporated into it, at the time of its construction, all the information about the tumor that it is possible to obtain. This may occasionally involve an elementary literature search or correspondence with the author of the data mentioning the new tumor, or with an authoritative source of tumor information in general. (E. g., if a tumor is added to the code at a time when information about its tissue origin is not at hand and the tissue origin code unit of the tumor symbol is assigned merely a series of Symbols 0, and then, if one year later information about the tumor's tissue origin is learned, the tumor symbol cannot be changed without recalling all coded chemical-biological data with which that tumor symbol had been used and altering each tumor code entry.)

The list of tumor symbols included in the Code were for the most part constructed by using information assembled by Dr. Lucia J. Dunham and Dr. Harold L. Stewart and published in 1953. (A Survey of Transplantable and Transmissible Tumors; Journal of the National Cancer Institute, Vol. 13, No. 5, April 1953, pp 1299-1377.) The authors pointed out in their introduction that it represented a first attempt and that subsequent information might be expected to reveal omissions. The CBCC code symbols for tumors of this list should always be reassessed in the light of any new information and appropriate changes should be made for any discrepancies with that new information.

It should be specifically understood that the pattern for constructing tumor code symbols is not intended merely for these transplantable and transmissible animal tumors. The objective has been to provide a scheme for coding any tumor. It is assumed that any tumor (including spontaneous tumors of clinical data) can be designated in Field E by constructing a symbol of seven or less digits (if it is not a specific, named, transplantable form) or of eight digits (if it is a specific, named, transplantable form), which will designate organ and tissue origin, when known. Many general types have already been included in the list (i. e., any of the items which are not actually named transplantable tumors), in the process of its organization.

CODING OF PATHOLOGIES

GENERAL DISCUSSION OF THE CBCC PATHOLOGY CODE

SECTION I: INTRODUCTION

1. General definition of pathology; restriction of pathologies in the CBCC Pathology Code

Disease or pathology is understood to define a condition deviating detrimentally from an anatomically or physiologically "normal" state. In general, disease originates (1) from an invasion of parasitic organisms (infectious diseases), (2) from damage by external physical forces (traumatic or radiation diseases, e.g.), (3) from insufficiency of any essential material such as a specific food, oxygen, vitamins, etc., (4) from chemical poisons, (5) from congenital defects, or (6) spontaneously from no known external cause (idiopathic diseases, such as those associated with aging, spontaneous atrophies and hypertrophies, certain inflammations, etc.). Distinction is made hereafter between infectious diseases and diseases of other etiological types (i.e., types by origin) by referring to the latter collectively as non-infectious diseases. This is by no means an absolute categorization; certain forms of disease, notably tumors, might have any of several possible origins.

In the Pathology Code of Field E, diseases of all etiological types are incorporated. The following observations should be made, however.

A. All tumors are organized into a special code for Field E, the Tumor Code, and therefore are not included with the items of the Pathology Code. In the Tumor Code, no provision is made for coding a tumor etiology specifically, even if known, although certain very general etiological information about a tumor can be coded by symbols provided in another field, Field F.

B. In the Pathology Code, the non-infectious diseases (defined above) are organized and assigned symbols as described in Section II.

C. Names of infectious diseases (defined above) are included in the Pathology Code list for convenience, but their symbols do not conform to the pattern for symbols of non-infectious diseases. Infectious diseases and their symbols, taken from the Taxonomy Code of Field E, are discussed later, in Division 2 of Section II.

2. Coding of non-infectious pathologies; factors determining the CBCC coding pattern

The most extensive and generally used classifications of diseases are to be found in the two publications, Standard Nomenclature of Diseases and Operations (American Medical Association)[1] and Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (World Health Organization)[2]. Both of these are the results of painstaking labor by highly qualified medical specialists. Because they claim different objectives, the two classifications are organized differently and their code symbols, though they are analogous, differ in structure and definition.

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1. Standard Nomenclature of Diseases and Operations, 4th Edition; R. J. Plunkett, M. D., Editor, and A. C. Hayden, R. R. L., Associate Editor; published for The American Medical Association; McGraw-Hill Book Co., Inc., 1952.

2. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Sixth Revision of the International Lists of Diseases and Causes of Death, Adopted 1948; Bulletin of the World Health Organization Supplement I, 1948.

While the excellence of these standard lists favored the CBCC's acceptance of symbols of one or the other for coding non-infectious pathologies, certain features did not recommend the adoption. The following four points are discussed here, since they describe factors that made adopting symbols of the classification schemes mentioned above inadvisable; at the same time, they are factors that influenced the development of the CBCC pattern of coding non-infectious pathologies.

A. The CBCC made the initial decision to use Field E to identify the specific causative organism (i. e., etiology) in coding information about chemical treatment of infectious diseases. Excluding infectious diseases reduced markedly the number of specific diseases for which a special Field E coding scheme would be needed to provide identifying code symbols.

B. It will be noted that the CBCC collects only information on experimental testing of chemicals on biological systems; furthermore, because some lines had to be drawn to make practical limitations to the coverage of which the CBCC was capable in the beginning, general clinical results have not as a rule been selected for coding. Even were clinical data to be comprehensively coded, the fact remains that, of the literally hundreds of specific conditions for which non-infectious pathology symbols may be constructed, only a limited number will be treated with chemicals experimentally, in spite of currently increasing chemotherapy practices.

C. Certain of the other fields of the Biology Code bear relationships to Field E so that information about a pathology is coded in them which otherwise would need be incorporated into the pathology symbol. Field T-2 exemplifies this, since a code entry in that field frequently supplements a pathology symbol coded in Field E. Thus, by virtue of having Field T-2, the CBCC Pathology Code has been relieved of the bulk of unique symbols which would be necessary for specific symptoms of diseases (e. g., hemorrhage of ovary due to scurvy; inflammation accompanying infection by a specific parasite; fever due to a specific poisoning; etc.). Likewise, use of Field H supplements pathology symbols so that frequently special symbols need not be constructed for the condition of each specific organ in a specific disease (e. g., eczema of the arm; effects of frostbite on blood vessels; effects on blood by hookworm infection; etc.).

D. A fourth factor that should be pointed out is that of limitation of space on a single IBM punched card. To leave coding space for all other factors of biological testing and confine biology coding to a single card, only eight places (i. e., only eight IBM punched card columns) were reserved for a symbol for a pathology (or test organism or tumor). The CBCC's purpose is primarily to record the results of experimental chemical treatment, using available space of a single punched card for that experimental data; it is not to record full descriptions of pathologies which might demand a coding scheme using an entire punched card. (See the second paragraph of Division 3 below.)

The factor of limited coding space on the IBM punched card, combined with the facts that the CBCC Biology Code would need only a limited number of non-infectious pathology terms and that these pathology terms would be supplemented by coding other than that in Field E, led to the formation of the special CBCC Pathology Code.

3. The CBCC pattern for coding identity of treated pathology is essentially a proposal, not actually tested by use

It must be emphasized that the CBCC has attempted coding very little information about experimental chemotherapy of non-infectious pathology. A list of pathologies was compiled in the initial stages of the development of the Biology Code to which symbols were assigned by a pattern that was subsequently lost or forgotten. When the few occasions arose to do so, identification of non-infectious pathologies was made according to this list. For practical reasons, that list has been abandoned. The present scheme for coding non-infectious diseases, prepared for this published edition, must be regarded only as a proposal which seems reasonable under the conditions impressed by the total CBCC coding pattern and which would seem to satisfy the needs of the CBCC for its stated objectives and scope of pathology coverage.

It is possible that, for effective coding treatment of non-infectious pathology, in a program dealing intensively or exhaustively with data from laboratory and clinical drug trials, a more elaborate pattern would be necessary. This might conceivably become comparable to the present CBCC handling of chemical structures, whereby a separate and special Code Sheet would be used for a given named pathology, an entire IBM punched card devoted to the pathology's complete description, and the identity of the pathology made on the general Biology Code Sheet only by a reference number comparable to the CBCC Chemical Serial Number. In any case, it would seem unlikely that the retrieval and correlation of information about responses of diseases to chemicals could be accomplished satisfactorily except by persons with some specific experience with the field of pathology and its nomenclature.

SECTION II:
CODE SYMBOLS FOR PATHOLOGY;
INFORMATION CODED IN FIELD E ABOUT
A SPECIFIC NON-INFECTIOUS PATHOLOGY

1. Symbols for NON-INFECTIOUS diseases; Part I of the pathology symbol (1st unit, Column 18)

Inasmuch as non-infectious pathologies are coded in the same field as any test organism or tumor may be coded, it is necessary that the Pathology Code symbol for non-infectious diseases be distinguished from symbols of the Taxonomy Code and the Tumor Code. For this purpose, the first of the eight units of the total non-infectious pathology symbol is always Symbol T. As a result, only seven units (i.e., seven IBM punched card columns) are actually available for symbols distinguishing pathologies of a non-infectious nature.

2. Symbols for INFECTIOUS diseases included in the Pathology Code list

When a pathology is caused by an organism (e.g., an invading bacterium, fungus, protozoan, or other parasite), that pathology is coded by using the symbol for the test organism taken from the Taxonomy Code list. Therefore, Symbol T, as the first unit of a symbol in Field E, signifies only disease of a non-infectious nature, as opposed to infectious diseases and tumors.

In the case of infectious diseases, there is no question about designating in Field E a coded anatomical association, since the entire coding area is occupied with the etiological identification. The disadvantage afforded by this is minimal, since, in the case of most infectious diseases, the anatomical designation would be the non-specific "body as a whole". However, in the case of certain infectious diseases or a given instance of any infectious disease, it is important to be able to provide critical identification by naming the site of infection. By the CBCC coding pattern, this can only be done by utilizing Field H as well as Field E. Thus, any infectious disease whose identity demands not only identification of the etiology as the organism in Field E, but identification of the anatomical site, is listed in the Pathology Code with the taxonomic symbol for the organism and the anatomical symbol for the site which must be coded in Field H (in Field H-1, if the site is identical to the specific organ responding, or in Field H-2, if it is not identical to the specific organ responding).

3. Part II of the non-infectious pathology symbol (2nd, 3rd, and 4th units, Columns 19, 20, and 21); the anatomical structures affected by the disease

Conventional pathology nomenclature, especially that for non-infectious pathologies, is based primarily on affected anatomy (i.e., site of the pathology). Therefore, pathologies are assigned code symbols according to an anatomical classification.

As pointed out previously, the anatomical site of an infectious pathology can never be indicated in Field E, because all eight IBM columns are occupied with the Taxonomy Code symbol of the infectious organism. The site of the infection can only be coded in Field H. For CBCC purposes, this coding is considered to be essentially adequate for distinguishing from each other all infectious diseases.

For non-infectious diseases, Field H is available for indicating the site of the pathology, just as for infectious diseases. However, a greater facility is offered by embodying the anatomical

classification in the Field E symbols for non-infectious pathologies. Therefore, the coding of the primary anatomical classification of non-infectious diseases has been shifted to Field E, using, however, the classification and symbols established in Field H.

This primary anatomical designation is the second part of the total Field E non-infectious pathology symbol, represented by the 2nd, 3rd, and 4th units (Columns 19, 20, and 21).

Coding of pathology in Field E has as its primary objective the identification of the specific condition treated, basing identity on anatomical and etiological relationships. Field H is used as a supplement to Field E in the case of pathology identification, in addition to being used to code the anatomical part specifically responding to the test compound.

4. Relation between the anatomical part of the non-infectious pathology symbol and Field H

In coding the identity of a pathology, coding in Field H indicates the location of the pathology, whether infectious or a tumor or even in the case of non-infectious pathologies whose primary or typical anatomical association is indicated in Field E. Field H-1 is coded with the organ responding to, or candidate for responding to, the chemical treatment and this is assumed to be the organ site of the pathology; however, if an organ responds which happens to be an organ other than the site of the treated pathology, the organ coded in Field H-1 will not represent the site of the pathology, the coding of which must be shifted to Field H-2.

Thus, two areas are available for coding non-infectious pathology sites, (1) Columns 19, 20, and 21 of Field E and (2) Field H, a feature lending versatility to code identification of infectious pathologies, as the following explains.

Many general non-infectious pathological conditions affect either the entire body or are non-specific and can affect any of a large number of sites; these particular conditions are assigned symbols with no specific site other than "body as a whole" (Symbol B00), indicated in Columns 19, 20, and 21 of Field E. When such a general pathology is restricted, in the case treated, to only a given anatomical part, the specific location can be coded in Field H. Certain pathologies may be primarily disorders of specific anatomical parts, coded in Columns 19, 20, and 21 of Field E, rather than of the entire body generally, yet, in the case treated, an organ which is secondarily affected by the disease (and which responds to chemical treatment) may be an organ of another type; the second organ can only be coded in Field H (see the third, fifth, and sixth of the following examples). The outline on the following page demonstrates these relations of Fields E and H in coding the anatomical aspects of pathologies, using liver disorders as an example. In these examples of identifying pathologies by code, attention is called to the anatomy entry in Field E (the part of the pathology symbol underlined) and the anatomy entry in Field H-1 and to the way these various combinations represent different statements of test conditions or results.

5. Part III of the Pathology Code symbol (5th and 6th units, Columns 22 and 23); etiology

Providing code symbols for specific pathological conditions is beset with problems arising from the nature of pathology and its resistance to classification. The organism is a physiological unit whose normal well being is dependent on the balanced and coordinated functioning of all its parts. When an initial disorder occurs, or when the organism is attacked by infection, the coordinate physiology is disrupted and a chain of subsidiary disorders may occur, contemporary with or subsequent to the initial disorder. The secondary disorders, while definable as entities, all too frequently bear characteristics peculiar to their origins in the primary disorder and, as a consequence, pathology nomenclature has evolved to embrace these origins in definitions.

In the case of both infectious and non-infectious diseases, each definition of a pathology in the Code list is made in terms of the origin of the disease, in addition to the anatomical site. For infectious diseases, the origin is defined by the symbol identifying the infecting organism, taken from Taxonomy Code.

When an item, included in the list of non-infectious pathologies, defines a pathological state that may have any of two or more known origins, it is assigned a symbol which identifies the disease

FIELD E; Pathology Code
Columns 18, 19, 20, 21,
22, 23, 24, and 25

CODING OF PATHOLOGY IDENTITY IN FIELDS E AND H (See Division 4.)			
Field E	Field H-1 Organ responding to chemical treatment. (If the pathological organ is not identical to the organ responding, code the organ pathological in Field H-2 and an asterisk in Col. 30.)	Field H-2 Organ pathological, if different from the organ responding (always accompanied with an asterisk in Col. 30 of Field H-1).	
(1) Chloroform poisoning: TB002600 (Pathology of the organism as a whole)	E (Liver)		This outline of procedure illustrates coding for: Any pathology, regardless of primary location, which has affected the liver and which is being treated by the test compound--or--situations in which the liver responds to the test compound, regardless of the location of the pathology treated.
(2) Yellow atrophy of the liver: TE10620G (Pathology of the liver)	E1 (Liver parenchyma)		
(3) Periarteritis nodosa: T325X200 (Any organ other than the liver; in this case, it is an artery)	E (Liver)		
(4) Syphilitic cirrhosis: JS902021 (No anatomical part; this is the symbol for the syphilis organism)	E (Liver)		
(5) Cirrhosis TE100002 (Pathology of the liver)	323 (Any organ other than the liver; in this particular example, it is the portal vein.)		This outline of procedure illustrates coding for: Any pathology specifically hepatic (regardless of primary location) which has affected other anatomical structures which are in turn affected by chemical treatment--or--situations in which organs other than the liver respond specifically to the test compound, although the condition treated is specifically hepatic.
(6) B_{12} deficiency (the liver specifically pathological and the portal vein affected by the test compound): TB00F900 (Pathology capable of affecting any of several organs)	$3^{*}_{2}3$ (Any organ other than the liver; in this particular example, it is the portal vein.) The organ affected specifically by the test compound.	E (Liver) (When accompanied with an asterisk in Col. 30 of Field H-1, this coding in Field H-2 represents the specific organ which is the site of the pathology coded in Field E.)	
(7) Clonorchiasis: 42103011 (No anatomical part; this is the symbol for the infecting trematode)	3^{*}_{3} (Any organ other than the liver; in this particular example, it is blood.) The organ affected specifically by the test compound.	E (Liver) (When accompanied with an asterisk in Col. 30 of Field H-1, this coding in Field H-2 represents the specific organ which is the site of the pathology coded in Field E.)	

anatomically only and which omits any etiological association; this is usually accompanied in the list by one or more items, each defining that state in which one of the possible known etiologies is specified and that specification is made in the symbol. Cirrhosis, for example, may have any of several recognized causes and cirrhosis is given a coding identity (by Parts II and IV of the symbol, Columns 19, 20, and 21 and 24 and 25) independent of the etiology (Part III, Columns 22 and 23). Cirrhosis is recognizable, therefore, even when no etiology is expressed (TE100002), as well as when it is due to a known cause (TE104202).

On the other hand, when an item is included in the list defining a non-Infectious state of whose origins medical science has no certain knowledge, it is assigned a definite etiological symbol specifying that (Symbol 7, G, P, or X, or 8, H, Q, or Y, in Column 22). All such diseases are given secondary classifications based on the anatomical effect of the disease or on the physiological action disrupted by the disease, whichever is the more characteristic manifestation of the pathology. Osteo-arthritis and rheumatic fever are examples of specific recognized diseases whose etiologies are still conjectural; the etiological symbols for those diseases specify this (T930710A and TB00G102, respectively).

Coding etiological factors has necessitated constructing a special list of etiologies to which diseases can be referred and from which symbols can be taken to construct unique Field E symbols for the Pathology Code. For this, the etiology organization of the American Medical Association "Standard Nomenclature of Diseases and Operations" has been used as a guide.

Columns 22 and 23 of Field E are designated for coding the etiology of a non-infectious pathology and these 4th and 5th units of the total Field E pathology symbol represent the third part of the symbol (i. e., the third category of information identifying and indexing diseases). The special list of etiologies and their symbols is included in the Code following the list of pathologies for which symbols have been constructed. While the classification itself can scarcely be described as provisional or unproved, since it is basically that of the AMA scheme, the proposed rather rudimentary adaptation should be regarded as candidate for further study and development.

By reference to the etiological classification in the Code, it will be seen that, in each of the eight major etiological categories, 140 symbols are available for specific etiologies. The basic symbol for each of the eight major categories is a numerical symbol in Column 22, Symbol 2, 3, 4, 5, 6, 7, 8, or 9. Each of the eight symbols can be combined with each of the three IBM zone punches to represent letter symbols. Thus, the first etiological category is represented in Column 22 by Symbol 2, Symbol B (the IBM punch in the "2" position plus the 12 zone punch), Symbol K (the 2 punch plus the 11 zone punch), and Symbol S (the 2 punch plus the 0 zone punch). The second category is represented by by Symbols 3, C, L, and T; the third category by Symbols 4, D, M, and U; and so on.

Symbol 1 has not been used in Column 22 for an etiological designation, because it can not be combined with the IBM 0 zone punch and given meaningful interpretation on the IBM equipment used by the CBCC and because the remaining symbols (2 through 9) have seemed adequate for all the etiological categories needed. The two etiological categories, infectious organisms and tumors, are omitted, because they are given special coding treatment, although the eighth category (Symbol 9 in Column 22) refers to an infectious agent in the history of a disease as being the typical initial pre-disposing factor to the disease by definition. In the latter case, since the organism is no longer present, the chemical treatment of such a disease is incapable of affecting the infectious organism as a living system, and the basic reason for identifying the disease by a Taxonomy Code symbol therefore does not exist.

Within a major category, the available symbols have in most cases been distributed to provide a reasonable secondary classification of etiologies. For example, within the fifth category, the symbols are divided among specific subcategories so that Symbol 6 in Column 22 is designated to specify metabolic disorders and toxins of metabolic origin as causes of pathology, Symbols F and Ø in Column 22 are assigned to specific deficiencies as causes of pathology, Symbols W1 through WR indicate endocrine functional abnormalities as causes of pathology, and Symbols WS through WZ indicate specific disorders in growth and development as causes of pathology.

It seems improbable that coded etiologies will be found a highly useful index for chemical-biological information, except in the case of infective organisms which represent specific "biological systems" against which chemicals may be administered experimentally. CBCC interests are centered on biological conditions specifically treated by and/or responding to (or caused by) chemicals. In the case of treated non-infectious pathological conditions, the origin of that pathology is of little significance, because it may be assumed that that initiating factor is not specifically treated or responding. Etiologies of non-infectious diseases are incorporated in the coding scheme presented here essentially because it has seemed the only reasonable solution to the problem of classifying and identifying by code specific named pathology states treated.

6. Part IV of the Pathology Code symbol (units 7 and 8, Columns 24 and 25)

Certain specific causes of disease produce such unvarying pathology pictures that identification of the causative factor is tantamount to identifying the disease; identifying infectious pathologies essentially by coding in Field E only the etiological agent (the infecting organism) is based on this concept.

However, in the reverse, there are a number of pathological states of given anatomical parts, distinguished as pathology entities by standard nomenclature, which may have any of several causes. To provide a fixed symbol for such a named pathology, regardless of the causative agent, Columns 24 and 25 are used for a coding distinction of diseases of the anatomical part coded in Columns 19, 20, and 21. Likewise, there are certain very general, yet uniquely named, pathological conditions that can be associated with almost any anatomical part and caused by many etiological factors.

Two types of entries are made in these final IBM columns of Field E, one being distinguished by use of only numerical entries in Column 25, the other by only letter symbols in Column 25.

Those entries of Columns 24 and 25 with only numerical symbols in Column 25 have no special meaning except to distinguish named diseases of a given anatomical structure which might not be distinguished by an etiology coded in Columns 22 and 23. For example, both "cough" and "dyspnea" are pathologies of the respiratory system and each may result from any of several causes. A symbol is constructed for each, with a nonspecific etiological part (Symbol 00 in Columns 22 and 23); the symbols for the two conditions are distinguished by assigning Symbol 01, in Columns 24 and 25, to "cough" and Symbol 02 for "dyspnea" (T500000**1** and T500000**2**, respectively). This type of entry which is distinguished by a numerical symbol in Column 25 has no "fixed" meaning. Thus, Symbol 01 in Columns 24 and 25 designates "cough", or "glaucoma", or "diarrhea", depending on the entry in Columns 19, 20, and 21. (Compare this with the second type of entry of Columns 24 and 25, which has a fixed meaning, described below.)

Subsequently, when a symbol is constructed for a cough due to any one specific cause, Symbol 01 in Columns 24 and 25 is used with Symbol 500 in Columns 19, 20, and 21 (invariably indicating "cough" when used together) and the nonspecific Symbol 00 in Columns 22 and 23 is substituted with the symbol for the cause. This will constitute a new entry in the Pathology Code.

By using two columns (24 and 25) and only numerical symbols in each, 99 named pathologies can be distinguished for each anatomical structure coded in Columns 19, 20, and 21, in addition to pathologies of that same anatomical structure which are adequately distinguished by coding only the etiological factor in Columns 22 and 23.

The second type of entry in Columns 24 and 25 (with letter symbols in Column 25) differs from the first in that each symbol is given a fixed meaning, regardless of either the anatomy entry in Columns 19, 20, and 21 or an etiological entry in Columns 22 and 23. These are ordinarily for certain general pathological states which can occur in many anatomical parts (or in any part) and which may have any one of many causes. A good example is the common "inflammation", which is always coded with Symbol 0A in Columns 24 and 25 when it is the chief manifestation of a disease, regardless of the site and etiology coded in Columns 19 through 23. A second such general condition, "shock", has been assigned Symbol 0B, "congestion" has been assigned Symbol 0C, etc. It is suggested that enough symbols for all such conditions needed by the CBCC (90 symbols) will be provided by using a single IBM zone punch, the 12 zone punch, so that only letters A through I should be used in Column 25, combined with any numerical symbol in Column 24.

SEX AND STAGE OF DEVELOPMENT OF THE TEST ORGANISM; MISCELLANEOUS INFORMATION CONCERNING TUMORS

Organization

In this field, the IBM zone punches 12 and 11 (coded as Symbols * and #, respectively) have been assigned special meanings, for which reason Symbols A through R (formed by the 12 or the 11 zone punch variously combined with the numerical punches 1 through 9) are unavailable for assignment.

Symbols S through Z (formed by using the final [0] IBM zone punch with the numerical punches) have been used for coding certain tumor features. Thus, these symbols can not be used for stages of development of a test organism.

As for the several lists of developmental stages, the definitions are arranged and assigned to Symbols 1 through 9 so that the youngest stage of development is represented by Symbol 1, followed by a step-wise progression to the oldest stage, assigned to Symbol 9. In the case of certain taxonomic groups, especially the lower plant forms, analogy with stages of other groups is not possible, since not only stages of one generation but of two or more generations needs distinction; however, an effort has been made to be consistent in retaining the gamete as a beginning point in life cycles. (The alternative would have been preparation of a list of stages for each generation of such an organism which is not practical for the CBCC purposes.)

General Use

The sex and stage of development of the test organism, at the time of treatment with the test compound, is coded in this field by use of Symbols 1 through 9 and * and #.

The sex and stage of development of host organisms is coded in Field K, rather than Field F.

The stage of the test organism when observed, if older than the stage treated with the test compound, is not coded (either in Field F or elsewhere).

If Field E is not coded with an organism but with a non-infectious pathology or tumor, Field F is not used except to code tumor information by use of Symbols S through Z, when appropriate.

Specific Directions and Explanations

1. Relationship between Fields F and E

Field F is used only to describe entries in Field E, either sex and stage of development of a test organism (Symbols * and # and 1 through 9) or information about a tumor coded in Field E (Symbols S through Z). Sex and stage of development of a host is never coded in Field F, but only in Field K.

2. Distinction between author's expressions of sex of organism used; coding of sex

If the author designates that only one sex is used, it is important that that sex be coded in Field F.

If the author indicates that "either sex" is used, code neither * nor # in Field F. I. e., do not arbitrarily code * or #, because that procedure is reserved for indicating that a sex distinction was made and has significance, and do not code both sexes in Field F, since if either sex satisfies the requirements of the test, the distinction is unnecessary and it furthermore permits reserving coding of both sexes for the following situation.

If the author specifies that, in a group of test organisms used in a single test, both sexes are used, there is an implication that the choice of both sexes has some significance. Therefore, this fact is coded by entering both of Symbols * and # in Column 26. (See also Division 4 below, describing double coding, which differs from the use of both Symbols * and # as just described.)

3. Stage of development to be coded in Field F

When the lapse of time between application of the test compound and the observation of response is of such duration that the test organism progresses from one developmental stage to another, the question arises as to whether there should be coded the stage given the test compound or the stage in which the response is manifest, since there is only one field (Field F) provided for this category of information. The CBCC has defined its single Field F to limit it to coding the stage at which the test compound was administered, which makes for consistency in the code statement describing the administration of the test compound--the dose recorded in Fields M and N, in the conditions recorded in Fields A, B, and C, by the route indicated by Field S-3, to the stage of the organism coded in Field F.

Unfortunately, the stage on which the observation is made (if later than the stage to which the compound is administered) can not be coded, because the CBCC has not felt that the few occasions when a second Field F would be needed for this justified reserving IBM space for it. The stage responding must be described in the written abstract portion of the field. The action coded in Field T and the evaluation time coded in Field V may sometimes suggest that the responding stage is a later stage than the one treated (Field F).

When Symbol Ø is coded in Field S-3, indicating that the test compound was applied to the parent, with the response (coded in Field T) observed on the offspring, the stage of development of the offspring at the time of application of the test compound, if known, is coded in Field F. (This is particularly in reference to viviparous organisms in which the developing young organism is exposed, just as an organ would be, to the test compound.) If the stage of development at the time of administration of the compound is not specified by the author, nothing will be coded in Field F, because Symbol Ø of Field S-3 describes the situation adequately.

4. Double coding of results from two or more tests with the only variable being sex or stage of development

If separate sexes are used in separate test runs and the only difference in the procedure is the sex of the organism and if the results of the tests are so similar that they can not be distinguished by the Code, a single code line is adequate for both tests, with Field F coded with Symbols * and #. (This combination of two or more tests in a single line, accomplished by a double entry in one field, is referred to as double coding.) The written abstract of Field F should record clearly the fact that the code line represents separate tests using different sexes rather than a single test using both sexes. The latter is described in Division 2.

If tests are made at each of several stages of development (the stages of development being the only variable in the tests) and the response and evaluation for all these tests are so nearly the same that they can not be distinguished by the Code, double coding with any of Symbols 1 through 9 is permitted. This double coding of stages does not interfere with double entry for both sexes in the same line. (See the last paragraph of Division 2.)

5. Use of Field F to record tumor information

When Field E has no test organism or infectious pathology coded in it (but is coded with a non-infectious pathology or tumor being treated), there is no need for a field to code sex or stage of development of the entry in Field E. Therefore, under those circumstances, Field F is free for describing another Field E entry, a treated tumor, and Symbols S through Z have been assigned for coding this information. (Since, under the circumstances when Symbols S through Z can be used, Field F would not be used for coding sex and stage of development of an organism, Symbols 1 through 8 might have been given second meanings--these tumor descriptions--so that when an organism was coded in Field E, Symbol 1, for example, would represent a stage of development, but when a tumor was coded in Field E, Symbol 1 would represent a characteristic of that tumor. To make interpretation of one field [in this case, Field F] dependent on the entry of another field [Field E] when it can be avoided, is impractical and it was for this reason that Symbols S through Z were chosen rather than

Symbols 1 through 8 [or A through H or J through Q, which represent IBM punches 1 through 8 plus one of the two zone punches, 11 and 12, used for another special purpose].)

6. Translation of size or age into stages of development

When the stage of development is not specified, but information is given concerning the size or age of the test organism, the following table may prove helpful in selecting the correct code symbol to be employed.

Code symbols for stages of development of test organisms.

Code Symbol	Organism				
	Rat	Mouse	Guinea Pig	Rabbit	Angiosperms
5	weanling <50 g <3 weeks	weanling <10 g <1-1/2 wks	weanling <100 g	weanling <300 g	Having no fully expanded leaves beyond the primaries (usually up to about two weeks after planting)
6	immature 50-150 g 3-9 wks	immature 10-15 g 1-1/2 wks	immature 100-250 g <10 wks	immature 300 g - 2 kg <7 mos	Vegetative; pre-flowering; young
7	("Adolescent", in stages of development of animals; applies literally only to man.)				Bearing flower primordia or macroscopic flowers
8	150 g and up (plateaued) >9 wks	15 g and up >5 wks	250 g and up >10 wks	2 kg and up >7 mos	Post-flowering; bearing fruit which may range from rudimentary to ripe and mature
	adult stage				
9	(senile; having lost the power of reproduction)				

7. Spermatophytes: further explanation of stages as defined in the Code

Symbol 1--indicating spore stage--is to be used to specify any stage of the haploid (gametophyte) generation of any of the spermatophytes (i. e., microspores, megaspores, pollen grains and the nuclei of the embryo sac in the angiosperms or the megagametophyte, microspores, megaspore or pollen grains in the gymnosperms).

Symbol 3--indicating embryo stage--is to be used to specify mature or immature embryos. Symbol 4 is to be used to indicate the mature embryo plus the seed coat (i. e., the complete seed). Symbol 3 indicates complete embryos (cotyledon[s], radicle, hypocotyl and epicotyl) and may also be used to indicate embryos from which some part has been excised. The excision of a portion of the embryo for discard is indicated in Field G-1 (or G-2) by Symbol P and the organ excised is specified in Field H-2 or the excision of a portion of the embryo to serve as the test organ is indicated in Field G-1 (or G-2) by Symbol R and the excised organ is specified in Field H-1.

8. Symbols available for additional items of Field F

In the present organization of Field F, all symbols have been assigned.

9. File of coded biology data on IBM punched cards arranged according to symbols for stage of development of the test organism or sex of the test organism or tumor character

The CBCC has not established a file of coded data (IBM punched cards) according to coding of Field F.

10. Double coding is permitted in Field F, as explained in Division 4. The two or more entries for sex and stage are punched on the same IBM card, as are the two or more symbols used in double coding either or both sex or/and stage.

FIELD G
(Field G-1) (Field G-2)
Column 27 Column 28

PRETREATMENT OR
EXPERIMENTAL STATE OF THE
TEST ORGANISM OR OF THE ORGAN,
TISSUE, OR CELL OF THE TEST ORGANISM

Symbol Z only:
EXPERIMENTAL TREATMENT OF THE TEST
ORGANISM OTHER THAN TREATMENT
WITH THE TEST COMPOUND AND
COMPOUND CODED IN FIELD D

General Use

1. Field G (Fields G-1 and G-2, considered collectively)

Field G is used to code any state or condition of the test organism, preparatory for or coincidental with the experiment with the test compound. Such a state may be the result of appropriate chemical or surgical pretreatment, it may be a naturally occurring special state selected for the experiment, or it may be a condition which the test organism has by coincidence. The field is never used to code a condition which is specifically treated by the test compound; such a condition is always coded in Field E, not in Field G.

In the following paragraphs discussing Field G, the expression "experimental state" is used in reference to those states or conditions (of the test organism or of the organ or tissue of the test organism) which are not being tested for a specific response to the test compound. Neither do these experimental states bring about a state or condition (i. e., a pathology) which is tested for response to the test compound.

The experimental states coded in Field G include results of operative procedures that are merely to facilitate the test or the observations of the responses. For example, an organ of the test organism may be denervated to isolate the organ functionally from nervous control. This denervation, as an operative procedure, is not a condition being specifically treated, for it is scarcely conceivable that the test compound could alter that specific fact of the nerve's being severed. The purpose of such an operation is to provide an organ whose response to the test compound will be exclusively chemical response and not complicated by nervous responses. In this case, denervation is coded in Field G (Symbol Q), the test organism to which the test organ belonged is coded in Field E, and the organ isolated is coded in Field H-1.

Included also among these experimental states are those indicating (1) that the test organism is of a selected type (e. g., a resistant strain or a sensitive strain), though the peculiarity of that type is not a condition being specifically treated, or (2) that the individual organism used deviates in some degree from normality (e. g., it has a nutrient or hormone deficiency, or it happens incidentally to have an infection, or it has been exposed to radiation, etc.), though this deviation is not a condition being specifically treated.

It is urged that the definitions of the field be studied, keeping in mind their use, since frequent coding errors occur due to misuse of the field, particularly in the case of beginning coders. A typical error occurs in coding a test compound's effect on a given hormone deficiency; an inexperienced coder

might code this specifically affected condition in Field G and the organism in Field E, whereas the condition should be coded in Field E (since it was specifically affected) and the organism should be coded in Field J as the host of the condition. On the other hand, if the test compound caused an effect (e. g., death or paralysis) on an organism which was reported to have a hormone deficiency, the coder might erroneously code the deficiency in Field E, whereas the effect was actually not on the hormone deficiency but on the test organism which should be coded in Field E, with the hormone deficiency coded in Field G.

Field G is restricted to expressing an experimental state or condition of the test organism in Field E (or of the test organism's organ or tissue in Field H-1 or I). It is not used to describe the host organism coded in Field J, since a separate field (Field L) is used for this purpose, nor does it apply to pathologies coded in Field E, except that Symbols F, G, H, I, and J (and possibly 6 and 8) may be used to distinguish infective diseases (i. e., to distinguish physiological strains of pathogenic test organisms). In the case of tumors coded in Field E, certain items of Field G might conceivably be applicable, if the tumor itself exhibited the experimental condition; if the experimental state is of the host of the tumor (coded in Field J), that condition must never be coded in Field G, but only in Field L.

In addition to the major purpose of Field G which the preceding paragraphs discuss, one symbol of the field, Symbol Z, has been provided for and restricted to another purpose. If the experimental factors (states) of Field G have been successfully defined, it will be understood that none of them is considered as part of the treatment of the test organism (in the way the test compound is the treatment), even though they may influence the outcome of the test. Symbol Z, however, is used to indicate a treatment of the test organism other than treatment with the test compound and secondary compounds and accompanying the treatment with the test compound. This single Field G symbol does not permit specifying the treatment (i. e., whether it was radiation, thermal, shock, etc.) so that if Symbol Z is used, the treatment must be specified in the written abstract of Field G-2. (Symbol Z is coded only in Field G-2 for sake of consistency.)

2. Fields G-1 and G-2, considered as separate fields

In order to record the presence of more than a single experimental state (a situation that frequently occurs), there are provided two places, both having the general Field G coding use, as described above. These are referred to as Field G-1 and Field G-2. If only one experimental state exists, it is coded in Field G-1. If a second state exists, it is coded in Field G-2. Field G-2, therefore, has no special use other than serving as a place to code a second condition when necessary. Since no space is available for coding more than two experimental states, a third can only be entered in the written abstract portion of the fields.

If a non-chemical treatment is given with the chemical treatment, Symbol Z is used in Field G-2, leaving only Field G-1 for coding states of the test organism.

3. Relationship of Field G to Fields E, H-1, H-2 and I

While it would be more simple, in terms of interrelations, to have separate fields for describing states of the test organism, states of the responding organ, states of organs other than the responding organ, and states of the responding tissues, several reasons make impractical having more than a single area (Fields G-1 and G-2) for coding these states. Therefore, coding in Field G can not specify whether it was the organism as a whole, or the organ in Field H-1, or the tissue in Field I (if all three fields have entries) that was given the pretreatment or that was in the state indicated by the Field G symbol, unless the symbol specifies by its definition that it was the organism, organ, or tissue. This is discussed again in Division 4 of the section on Specific Directions and Explanations below.

Field H-2 is used to supplement the coding of Field G in describing certain pretreatments or states (Symbols Ø, P, B, S, and T) of entries in Fields E, H-1 and I.

4. Significance of information about experimental states coded in Field G

In most cases, responses to the test compound depend upon, or are modified by, the experimental state so that if that state were not present, the response would be to some degree different or might even not occur. Therefore, it is frequently of importance and is sometimes of such importance

that, if omitted, the total code line would be misleading. It is for this reason that Field G is provided for recording any experimental state of the test organism.

Specific Directions and Explanations

1. Field G is related exclusively to Field E, NOT to Field J

As explained more fully in the previous section, General Use of Field G, this field is used exclusively for:

A. Describing entries in Field E (or the organ or tissue [Fields H or I] of that entry in Field E), usually test organisms, --

B. Describing conditions that, in a sense, are incidental in that they are not themselves being specifically treated, and--

C. Indicating experimental treatment of the test organism (Field E) other than treatment with the test compound and compound coded in Field D (Symbol Z only).

2. Coding when presence of a tumor is incidental

When a test organism, coded in Field E, has a spontaneous tumor and the information being coded is unrelated to any response of the tumor to the test compound, the tumor's presence is merely incidental and should be coded in Field G with Symbol 7, N, or Ø, but not with Symbol 5. (If the incidental tumor is not spontaneous, but implanted, use Symbol S.)

3. Use of Field G-1 or both Fields G-1 and G-2

When there is present only one experimental state, code this in Field G-1; when there are two such conditions, code either of them in Field G-1 and the remaining condition in Field G-2, except that Symbol Z should always be coded in Field G-2. (See Division 17.)

4. Use of Field G (both Fields G-1 and G-2) relative to Fields E, H-1, H-2, and I

A. Field H-2

In the description of Field H, it is explained that Field H-2 is used only to code an organ that is not an organ specifically responding to the test compound. (An organ specifically responding to the test compound is invariably coded in Field H-1.) This organ in Field H-2 may be an organ to which the test compound was applied when application was not to an organ specifically responding to the test compound (i.e., when application was not to an organ coded in Field H-1). However, Field H-2 is also used with Symbols Ø and P (and infrequently with Symbols B, S, and T) of Field G in describing those states of the test organism, organ, or tissue specifically responding to the test compound.

B. Fields E, H-1, and I

Division 3 of the section on General Use has described basically the relationship between Field G and Fields E, H-1, and I. Field G is used to describe (a) a state of the test organism or (b) a state of an organ which responds specifically to the test compound (and is therefore coded in Field H-1), or (c) a state of a tissue which responds specifically to the test compound (and is therefore coded in Field I).

Certain of the items of Field G are defined so that any one of them may represent a pretreatment (and the experimental state) of the test organism OR a pretreatment specifically to the organ coded in Field H-1 OR to the tissue in Field I. This is particularly true of those pretreatments (experimental states) coded by Symbols 1, 2, 3, 4, and M. For example, by coding Field G with Symbol 4 when Fields H-1 and I are coded, there is no indication thereby as to whether the organism as a whole was

exposed to radiation (Field E), or whether radiation was given directly and specifically to the organ in Field H-1 or to the tissue in Field I. Symbols N, Q, R, T, U, V, W, and X do not distinguish as to whether the pretreatments (states) coded by these symbols apply to the organ in Field H-1 or to the tissue in Field I (if both Fields H-1 and I are coded) except that it is probable in most instances that when a tissue is given pretreatment or is in a special state, the organ of which it is a part received the pretreatment or is in the same state. The same is true for Symbols 6, 8, B, C, D, E, J, and S, except that the pretreatments (states) coded by these symbols are by their nature apt to be restricted to refer to the organism as a whole. (The remaining symbols, 5, 7, 9, A, F, G, H, I, K, L, Ø and P, present no problem in reference to Fields E, H-1, and I, since the relationship is implicit in their definitions.)

The ambiguity of reference of the symbols named could be avoided either by multiplying the number of symbols of the field (e.g., three symbols for radiation instead of only Symbol 4, one for use when the organism as a whole is radiated, one for the radiation of the organ in Field H-1, and a third for radiation of the tissue in Field I) or by having a Field G equivalent for each of Fields E, H-1, and I. Since neither of these has seemed practical for the CBCC, the coding of Field G can be no more specific than the definitions imply. Therefore, when Field H-1 has an entry (with no entry in Field I) and Field G is coded with any of Symbols 1, 2, 3, 4, 6, 8, B, C, D, E, J, M, or S, or when Fields H-1 and I are both coded and Field G is coded with any of Symbols 1, 2, 3, 4, 6, 8, B, C, D, E, J, M, N, Q, R, S, T, U, V, W, or X, reference must be made to the written abstract on the code sheet to ascertain whether it was the organism as a whole, the organ in Field H-1, or the tissue in Field I to which the pretreatment was given or which is in the state indicated by the symbol.

5. Conflicts in Field H-2

Field H-2 has been endowed with two major uses and a third infrequent use. (See Divisions 2, 3, and 4 of the section, General Use, of Fields H-1 and H-2 and Divisions 1 and 2 of the section, Specific Directions and Explanations, of Fields H-1 and H-2.) For this reason, if Field H-2 should be needed for more than one of these uses in a single code line, it is necessary to follow an established pattern of preference to permit correct interpretation of the coding. These conflicts of Field H-2 are discussed in Division 3 of Specific Directions and Explanations of Fields H-1 and H-2. In short, any organ specifically responding to the test compound which is not coded in Field H-1, but is coded in Field H-2, with an asterisk (the 12 zone punch) in Column 30, is given preference over any other use of Field H-2. An organ in a special experimental state (indicated by Field G-1 or G-2) is given preference over an organ to which the test compound is administered (coded in Field S-3). Any organ that can not be coded in Field H-2, because of such a conflict, must be carefully recorded in the written abstract of Field G or Field S-3.

In interpreting coding of Field H-2, note first if Column 30 has a 12 zone punch; if there is none, note whether any of Symbols Ø, P, B, S, or T are coded in Field G-1 or G-2. If so, the Field H-2 entry is an organ in the state described by that Field G symbol; if not, it is an organ to which the test compound was administered as described by the symbol in Field S-3.

6. An incidental pathological condition vs. a TREATED pathology

The Symbols 5, 7, B, C, D, N, Ø, and S are not used when the pathological conditions that these items can suggest are coded in Field E. These code symbols are used only when the pathological condition is incidental (i.e., is not being treated) and, therefore, is not coded in Field E.

7. Adaptations (Symbol 1)

Especially in the case of tests in the laboratory, animals must often become familiar with their surroundings and handling before they are tractable or can respond suitably to treatment. Such conditioning of plants to laboratory conditions for certain tests is not unusual. If this, or any adaptation, is described by the author as an important factor, it should be indicated by Symbol 1.

8. Nutrient and hormone deficiencies and excesses, as incidental conditions vs. treated conditions

The code symbols, B (hormone deficient), C (hormone excess), D (nutrient deficient), and E (state of inanition), are used when the deficiencies or excesses are NOT the specific diseases treated.

In such cases, these conditions are subsidiary factors of the test preparation being treated and are properly coded in Field G. If, however, these deficiencies or excesses represent the pathology which is affected by the test compound, the condition is to be coded in Field E.

Field G is not used to record an experimental procedure used to bring about a pathological condition coded in Field E. For example, if an endocrine gland is removed to bring about an endocrine deficiency which is to be experimentally treated, the endocrine deficiency is coded in Field E, but the gland's extirpation is not coded in Field G (with Symbol B), because this operation is not incidental but is (or brings about) the condition treated.

9. Symbol F of Field G is used to distinguish two code lines representing collective data from more than two tests using several test organism strains

(Refer to Part I, Division 4, under the special section on Specific Directions and Explanations for the Taxonomy Code of Field E.) The CBCC has used Symbol F in a special way somewhat contradictory to the definition which states that its use is restricted to indicating that a special taxonomic strain has been used in the test: it is used in the situation when a number of strains (either taxonomically or physiologically distinct) have been tested by the identical test method with a given test compound for a given response and some strains have responded while some have not, or some strains have given a positive response while others have given a negative response, or some strains have given a positive response of another level, etc. A single code line is customarily constructed for all those strains showing the response and a single, second line is constructed for all those strains showing no response or the opposing response. In the second of these lines, Field G is coded with Symbol F as a standard means of distinguishing the two lines and explaining the difference between the two in their evaluation fields. If responses of all of the responding varieties (coded by the first line) fall within the same range of effectiveness (i. e., all their evaluations are coded by the same symbol in Field Y), Field Y will be coded with that symbol, but if they do not all fall in the same range of effectiveness, code only the response of the strain that seems most significant (if that can be determined) or code Field Y only with Symbol 0.

A single symbol can distinguish no more than two lines: Symbol F can be used only to distinguish (1) two lines, the first coding responding strains vs. a second coding non-responding strains, or (2) two lines, the first coding strains responding positively (i. e., an increase over normal) vs. a second coding strains responding negatively (i. e., a decrease over normal). It is for these two purposes that the CBCC uses Symbol F as a distinguishing symbol. Symbol F might also be used in a third or fourth way: to distinguish (3) two lines coding strains responding at two distinct positive levels (i. e., increase over normal of 81-90%, coded by Symbol 8 in Field Y vs. increase over normal of 41-50%, coded by Symbol 4 in Field Y) or (4) two lines coding strains responding at two distinct negative levels; however, relative to the last two possible uses of Symbol F, the CBCC has always coded data of strains responding positively at two levels (or negatively at two levels) by combining them in a single line with Symbol 0 or 1 in Field Y, merely as a means of saving coding time and space. In any case, those third and fourth uses of Symbol F could be made principally when only two strains are involved, simply because when several strains are tested, their responses seldom are so obliging as to fall in only two distinct scales of evaluation (although it is possible that they may and in that case Symbol F might be used to distinguish them); there is no way of distinguishing results which are at three or more distinct levels--i. e., falling in three or more evaluation scales (e. g., 81-90%, 41-50%, and 1-10% responses): to combine two of these in a second line with Field Y coded with Symbol 0 would be meaningless as a coding distinction from the first line and to code three lines with Symbol F in Field G of two of the lines would be equally meaningless.

The two facts, (1) that the first line, of such pairs of lines, does not have coded in Field G that the test organism is a special strain and (2) the lack of any means of indicating in either line (nor on either IBM punched card) that it has a companion code line (or a companion IBM punched card) is no problem largely because any search in the files will retrieve both IBM cards which will lead to both code lines with the information about the strains responding.

An alternative to this use of Field G for distinguishing strains in a non-specific way would be the addition to Field E of specific strain designations, thus permitting a code line and an IBM punched card for each test using a special strain. The infrequency of the CBCC's need for distinguishing special strains justifies not distinguishing strains in Field E and contending with occasional coding of non-specific strain designations as described above.

10. Pretreatments represented by Symbols 2, P, Q, and R; distinctions of definitions and use of the four symbols

Symbols 2, P, Q, and R represent experimental states that are often particularly significant and their use deserves some explanatory discussion. These conditions are the result of deliberate chemical or surgical pretreatments which are preparatory for the experiment with the test compound. Such pretreatments might all have been assigned a single code symbol with the general definition "chemical or surgical pretreatment of the organism or organ". However, since there is advantage in being more specific, the pretreatments have been further classified into four types. For clarity in distinction, Symbols P, Q, and R are described prior to Symbol 2.

NOTE THAT SYMBOLS 2, P, Q, and R, as well as all other symbols of Field G (with the exception of Symbol Z), DESCRIBE ONLY PRETREATMENTS, according to the symbols' definitions, AND NEVER DESCRIBE A TREATMENT COMPARABLE TO THE TREATMENT WITH THE TEST COMPOUND. If, for example, the removal of an organ or a tissue is in part responsible for the action coded in Field T-2 (i. e., if the response coded in Field T-2 is due to surgical treatment as well as treatment with the test compound), the surgical treatment can not be indicated by Symbols 2, P, Q, or R, nor can it be coded specifically by any symbol. Only by Symbol Z can the fact be coded that the test compound is not entirely responsible for the action and that another, non-chemical treatment was in part responsible.

A. Symbols P, Q, and R

The objective of the pretreatments included here is the isolation of the organism or organ from one or more physiological factors that normally influence it. Examples of such pretreatments illustrate the distinction in uses of the three symbols, as follows:

Symbol P (test compound action on the organism or organism part OTHER THAN the organ isolated):

(1) Isolation of the organism from the influence of one or more of its specific parts by extirpation of that part, such as removal of the spleen. The excised organ is not coded in Field H-1, because it is not an organ responding to treatment with the test compound, but is a discarded organ; what remains of the organism is treated with the test compound. (The excised organ is coded, however, in Field H-2.)

(2) Isolation of the organism from the activity of a specific organ left in situ. This is possible by selectively cutting or drugging the nerve supply of that organ, e. g. The organ rendered functionless is coded in Field H-2 (never in Field H-1). If the in situ preparation is accomplished by blocking or destroying nerves or blood vessels of the organ, the nerves or blood vessels can not be coded, but the procedure should be in the written abstract of Field G. On the other hand, if the organ rendered functionless is a specific nerve or group of nerves or a blood vessel, instead of an organ served by the nerve or vessel, it is coded in Field H-2 and it is understood that all effects of that nerve or blood vessel on all organs supplied by it are thereby abolished.

The removal of a gland to produce a specific incidental hormonal deficiency (i. e., a hormone deficiency not specifically treated by the test compound) would be coded by Symbol P except that a special symbol for this particular condition is provided (Symbol B) and should always be used rather than Symbol P.

Symbol Q (test compound action on the in situ organ isolated):

In situ isolation of the organ coded in Field H-1. This includes the isolation of an organ from material it ordinarily processes, such as the short-circuiting of food around an isolated experimental part of the alimentary tract (Pavlov pouch, intestinal loop, etc.). It also includes isolation of an organ from the body as a whole, such as severing or freezing the nerve supplying the organ or blood circulating to the organ (the nerve or blood vessel of which preparation would not be coded in Field H-2).

Symbol R (test compound action on the excised organ isolated):

Isolation of the organ coded in Field H-1, by EXCISION. For example, the removal of a turtle heart on which the action of the test compound is to be investigated, by perfusing it with test compound solutions; the fact that this heart is isolated and excised is coded with Symbol R in Field G.

The preparations described by Symbols P, Q, and R are made because the isolation removes physiological factors from the organism or from the organ, as the case may be, which if present would mask wholly the effect of the test compound or would make extremely difficult the evaluation of the test compound's effect.

The general definitions of the three symbols, P, Q, and R, are summarized by the following scheme. The symbols represent pretreatment which has as its objective:

(1) The isolation of the organism (Symbol P) from the influence of one or more of its specific parts (the part being left in situ or excised), or--

(2) The isolation of the organ (Symbols Q and R) from one or more of its specific parts, from material it normally processes, or from the organism of which it is a part. (Symbol Q is used to code the isolation of an organ in situ; Symbol R is used to code the isolation of an organ by excision.)

When coding excised muscle-nerve preparations (see Division 8 of the Specific Directions and Explanations for Field H for a discussion of provisions for this), Symbol R is used in Field G. If the muscle-nerve or gland-nerve preparation is not excised or if the organ-nerve pair is isolated only by the nerve being sectioned, Symbol Q should be used in Field G. The standard heart-lung preparation requires the use of Symbol Q, since the organs are essentially not excised.

B. Symbol 2

Any chemical, surgical, or electric shock pretreatment which does NOT have the objective of isolating the organism or the organ is coded by Symbol 2 (in contrast to the pretreatment indicated by Symbols P, Q, and R, as described above). This excludes, however, pretreatments by exposures to abnormal chemical or physical environments, Symbols 1, 3, 4, etc. Included would be applications of dyes for visual distinctions, surgical exposure merely for observation, and any other special surgical or chemical preparations not adequately described by one of Symbols P, Q, or R. General anesthesia would also be coded by this symbol, but the CBCC has refrained from designating it, even when it is specifically mentioned by the author, because it is considered a common technical procedure which is assumed to have no significance relative to the outcome of the specific response to the test compound. If, however, the presence of the anesthesia were on some occasion demonstrated to have such significance, it should be indicated without fail by Symbol 2 in Field G.

C. Chemical pretreatment is not equivalent to treatment with a secondary compound

Any chemical pretreatment indicated by Symbol 2, P, or Q, is not in any way an interaction with the test compound (as pretreatment with a secondary compound or a test compound would be); it is merely an experimental technique permitting the response to the test compound to be revealed by removing factors that would obscure that response, or a technique for staining or observing an organ or tissue, or for quieting the animal or desensitizing it to pain, etc.

D. The experimental state of physiological stress excluded from definitions of Symbols 2, P, Q, and R; stress coded by specific symbols

Any pretreatment, whether chemical or surgical, which has as its objective the production

of experimental physiological stress should be coded by Symbol N, Ø, or 7, not by Symbol 2, P, Q, or R. (E.g., application of a hormone excess to cause a stress which is itself not the condition being treated would be coded by Symbol N, Ø, or 7 and not by Symbol 2 or C; a surgical excision of an organ or one of a pair of organs to produce a stress which is not the condition being treated would be coded by Symbol N, Ø, or 7, not by Symbol P.) For example, if one kidney is removed to produce experimental stress on the remaining kidney, "kidney" is coded in Field H-1 (with Symbol N in Field G) as the organ under stress (if the kidney is also the organ responding to the test compound) or in Field H-2 (with Symbol Ø in Field G) as the organ under stress (if the kidney is not the organ specifically responding to the test compound or if the general organism response rather than a specific organ's response is being coded).

11. Use of Symbols 6 and J; STATES OF resistance to, or sensitivity to, the test compound vs. PRODUCTION OF THOSE STATES

A. STATES of the test organism

(1) Sensitivity (Symbol 6)

(Biological "sensitivity" to a chemical is the responsiveness of an organism to a chemical; i.e., any "action" of a test compound can be also described as due to a responsiveness or sensitivity of the test organism. A "produced sensitivity" or "increased sensitivity" [including "sensitization"] is a phenomenon which is not evinced on an initial exposure but is brought about by some biochemical adjustment during the first exposure.)

When a test organism develops a sensitivity to a test compound on exposure to that compound, the sensitivity is not revealed except by an application subsequent to that initial application. (This is self-evident, by definition, since if the sensitivity had been present at the initial exposure, it would not have been a "developed sensitivity", but merely a test organism "response".) The CBCC codes the production of sensitivity in Field T as an action of that first exposure (Field T-2 symbols of the 51-- series and Symbol 58), even though evidence is from subsequent administrations. The actual sensitive response can not be coded in the code line which codes the first exposure to the test compound, since the response did not appear except on subsequent exposures. This is discussed also in Division 11 of the Specific Directions and Explanations for Fields M and N, and in Division 20 of the Specific Directions and Explanations for Field T-2.

However, if a code line is constructed in which are actually coded in Field T the responses caused by or affected by the induced hypersensitivity, it is essential that Field G be coded with Symbol 6 to indicate that the response or degree of response was due to a previous exposure to the test compound (or to a secondary compound which caused a cross-sensitivity to the test compound).

(2) Resistance (Symbol J)

When a test organism has been made refractory to the action of a test compound, prior to treatment with that compound in the test being coded, that response to the test compound will consequently be less than in an organism not having been so pretreated. Therefore, it is important that Field G be coded with Symbol J to indicate that the response and degree of response should be interpreted in the light of the results of that previous exposure to the test compound which has stimulated a resistance in the test organism (or a previous exposure to a secondary compound, or to an infectious organism that elaborated that secondary compound, which has caused a cross-resistance to the the test compound).

B. PRODUCTION OF the states of resistance and sensitivity

The production of resistance or sensitivity to a test compound is only revealed by exposures

subsequent to an initial exposure. The CBCC, however, codes the description of the initial exposure that produced the resistance or sensitivity. Therefore, when coding these actions (Field T-2, symbol series 51-- and Symbol 58), Field G is never coded with Symbols 6 or J, since at the time of that initial exposure (when the resistance or sensitivity was produced), the state of resistance or sensitivity did not exist.

12. Symbols F, G, H, and I represent characteristics intrinsic to the test organism and do not represent responses to the test compound

Symbol G is not used when coding the production of cross tolerance by a test compound. Symbols F, G, H, and I are used only for strains that have naturally the attributes indicated or that have acquired the attributes prior to the experiment with the test compound, not for individuals made resistant, sensitive, dependent, etc., during the course of the treatment being coded.

As indicated in the definition for Symbol G, the four symbols, F, G, H, and I, are for distinguishing physiological strains only (such as "resistant strain", "sensitive strain", etc.). They are never used to distinguish a taxonomic strain (a breed of dogs or cows, a strain of bacteria, etc.). The CBCC Code does not distinguish taxonomic strains of test organisms and when a strain is given a special symbol in the Taxonomy Code, it represents an exception for which there has seemed adequate justification. The special use of Symbol F, described in Division 9, is not an exception to never indicating taxonomic strains by Field G, since it permits distinguishing a group of responding taxonomic strains from a group of unresponding taxonomic strains and therefore is really distinguishing organisms by a physiological characteristic.

Occasionally, even a physiological strain can be given a special symbol in the Taxonomy Code (e.g., the DDT-resistant housefly). Symbols F, G, H, and I need not be used if the test organism is of a physiological strain (resistant, sensitive, etc.) which is already adequately indicated by a special distinguishing symbol in Field E.

13. Test organisms, organs, or tissues WITH INCIDENTAL IMPLANTS

Symbol S is used to indicate that the organism, organ, or tissue responding to the test compound has incidentally a structure implanted in it, regardless of whether the implanted structure is normal, a tumor, or a pathological structure, or causes a pathology, as long as the response of that implant to the test compound is not being coded. For example: There are reported observations on a compound's toxicity to mice with tumor implants (the tumors having been treated with the compound as a candidate carcinostat). In coding the toxicity, the mouse is coded in Field E, the toxicity response in Fields T, X, and Y, and Field G is coded with Symbol S.

14. Test organs or tissues incidentally IMPLANTED into organisms, organs, or tissues

Symbol T is used to code the implantation of a normal organ, tissue, or cell into another organism, organ, or tissue, when the response of the implanted organ, tissue, or cell to the test compound is being coded and when Field J is not coded because the implant and the organism receiving it may be considered as a normal biological unit rather than as a host-parasite or host-pathology relationship. Since these implanted structures are the responding structures (and their implantation is their experimental state), they will be coded in Fields H-1 or I. This situation is given definition here and assigned Symbol T for sake of completeness, though it is improbable that frequent occasions will arise to use it. Symbol T might be used if chemicals are tested as means of making an implant successful; tissue grafts or organ implants, either embryonic or adult, might be given local chemical applications which would be candidate to assist the implant in establishing. (In this example, Field T would be coded to indicate prevention, by the test compound, of the atrophy or other fate the untreated implant would meet; Field G would be coded with Symbol T to indicate that the organ or tissue in Field H-1 or I was an implant.)

(When the implanted structure is [1] not normal, i.e., is [a] a tumor or [b] otherwise pathological or [2] if the implant brings about a pathological condition and there is being coded the response [to the test compound] of that tumor or of the pathology of the implant or of the pathology caused by the implant, the tumor or pathology will be coded in Field E and Field G will not be coded with Symbol T.)

15. Indications that an extirpated test organ or tissue is whole (Symbol R) vs. the indication that the test organ or tissue has been macerated, sliced, etc. (Symbols U, V, W, and X)

Symbol R is used to code the isolation of a whole organ (e. g., the heart), a representative section of tissue (e. g., liver tissue), a cell (e. g., a neuron), or a representative sample of fluid (e. g., whole blood), which is subsequently treated. Symbols U, V, W, and X, on the other hand, are used to describe specific experimental preparations following any isolation. For example, an isolated tissue might be macerated to a suspension (Symbol U), filtered for the extract (Symbol V), or subsequently grown on culture media (Symbol W), or micro-sliced (Symbol X).

The manipulation of the tissues, implied by Symbols U, V, W, and X, represents the beginning of a preparation which may be preceded or followed, after some time interval, by introduction of the test compound. Time intervals such as this are ordinarily coded in Field R. For example, the time interval between (a) preparation of a TISSUE (Symbol U, V, W, or X in Field G) for an enzyme study and (b) the introduction of the test compound may be significant and, if given, warrants recording in Field R.

16. Symbols U, V, W, and X describe states of the test organism, organ, or tissue at the time of the chemical treatment

When a compound is applied to an organism or organ which is later homogenized or made into slices or extracts, etc., for purpose of reading the test results, Code Symbols U, V, W, and X can not be coded in Field G. This field is used only to describe the state or condition of the test organism at the time of the treatment.

17. Symbol Z (Field G-2 only)

This symbol is used in a unique way and does not correspond to the other symbols of Field G in that it does not represent just a state of the organism during the test, but it represents, like the test compound, an active factor of the treatment. When this symbol is used, it indicates a treatment used on the test organism (which may be in any experimental state indicated by any of Symbols 1 through X), in conjunction with the test compound treatment (or test compound and secondary compound treatment). (See the first division [last paragraph] of the section on General Use of Field G.) Symbol Z is coded only in Field G-2, for sake of consistency, and must be coded in any such test which includes non-chemical treatment as defined in the Code. Symbol Z takes priority over Symbols 1 through X in Field G-2.

18. Symbols available for additional items of Field G

All numerical and letter symbols available for Field G have been used, with the exception of Symbol Y.

19. File of coded biology data on IBM punched cards arranged according to symbols for experimental states

The CBCC has established no special file of coded data in which Field G has been used (and arranged by Field G symbol sequence), because of the remote probabilities of a frequent need to search for all information on tests in which was a specific incidental condition of the test organism.

20. Double coding is not possible in Fields G-1 and G-2

Having made use of all of numbers 1 through 9 and all 26 letters for code symbols in Field G, the IBM machine punching and retrieval procedures do not permit more than a single symbol in Field G in any one line. Therefore, when coding two or more tests whose details and outcomes are so nearly alike that the code lines for all tests would be identical except for differences in pretreatment or state of the test organism (Field G), the tests can not all be recorded by one code line with several entries (representing the several pretreatments or states) in a single column (either Field G-1 or Field G-2). (A special circumstance allows condensing two or more tests in a single line by use of Symbol F of Field G [explained in Division 9], but this is not strictly comparable to double coding as it is described in the preceding sentence and even in this special case, Field G is occupied with but a single symbol.)

FIELD H-1
Columns 29, 30, and 31

FIELD H-2
Columns 32, 33, and 34

GROSS ANATOMICAL STRUCTURE: ORGAN, SYSTEM, BODY AREA

Organization

In this area of the CBCC Biology Code, six columns of the IBM punched card (and the Biology Code Sheet) are divided into two fields of three columns each, designated as Field H-1 and Field H-2. In the Code, there is a single list of anatomical structures, the symbols of which may be used for coding either field. Due in part to the limitations of space on a single punched card and in part to the complexity of anatomical classification, a single symbol has in some cases been given a definition to include homologies as well as analogies. For example, Symbol B61 can apply to any of the following: arm, wing, pectoral fin; paw, hand; or any other vertebrate anterior appendage or part thereof; Symbol 512 can be used for: spiracle, respiratory pore, or nostril. This presents no difficulty in interpretation, since the organism to which the structure belongs is identified in Field E or Field J.

The first unit of the three-unit anatomy symbol represents the general system of which the structure is a part. When used alone, this unit represents the complete symbol for the system (e.g., Symbol 1 in Column 29 or Column 32 represents the nervous system). The second unit represents a subdivision of a system (e.g., central nervous system, Symbol 15) or it may represent a discrete organ of a system (e.g., stomach, Symbol 66). The third unit distinguishes the least anatomical structural division of this field, whether it is an organ (e.g., the spleen, Symbol 342) or whether it is an organ part (e.g., the stomach cardia, Symbol 662).

Subsequent to preparing the initial list for the field, items have been added as they were needed. This is done by simply giving the new item a symbol whose first unit represents the system to which it belongs and whose second and third units are the next available sequential numbers or letters. For example, the symbols for right and left auricles might be expected to be 312 and 313, since the symbol for auricle is 311; however, since these structures were given distinguishing symbols after Symbols 312 through 31C had been used, they were assigned Symbols 31D and 31E.

The procedure for adding new items to the list may result in the structure being listed distant from structures to which it is most nearly related. (In the example cited above, the right auricle is listed as a distinct item, Symbol 31D, 11 items away from auricle, Symbol 311.) These items are listed again, merely for convenience, with the related structures. (Therefore, Symbols 31D and 31E will be found between the Symbols 311 and 312, as well as after Symbol 31C.

Because certain organs, especially specific nerves and blood vessels, form an integral part of organs or systems, other than the system to which they actually belong, they are frequently listed twice, with the organ or system they supply as well as with the system to which they belong. For example, the optic nerve is listed both with the cranial nerves (symbol series 13) and with the eye structures (symbol series 21), although its symbol is always 133 regardless of where it is listed. Similarly, certain gross organs are constituted of glandular components as well as non-glandular parts. The glandular structure or part of such an organ is assigned a symbol of the C or D series (according to whether it is endocrine or exocrine) and this symbol and structure is listed both with other glandular structures and with the gross organ of which it is a part. (Examples will be found in the reproductive organ list, symbol series 8.) This double listing is merely for convenience.

The list is hardly an exhaustive compilation. It might be expanded for special purposes and for data from new areas of investigation. For example, additional items might be needed under the autonomic nervous system and central nervous system for data from investigations on the tranquilizing drugs.

The 12 zone punch (coded by Symbol *) has been given a special meaning when used in IBM Column 30. (See the following section, General Use.) For this reason, none of letters A through I can be used for the second unit of symbols in Field H.

General Use

In the case of many tests for biological responses to chemicals, specific anatomical parts of the organisms involved represent significant aspects of the test method or response. The area of the Code that is devoted to expressing these specific structures comprises Field H-1 and Field H-2, for gross anatomical parts, and Field I, for tissue and cellular parts. Although this section, as well as the following section on Specific Directions and Explanations, concerns principally Fields H-1 and H-2 (gross anatomy), Field I (microanatomy) will frequently be mentioned with them; the three fields together make a unit for coding of structural parts, since the relationships of each of the three fields to other fields of the Code are essentially identical.

There are two fields in which an organism may be coded: Field E, for the test organism, and Field J for the host organism. Since the CBCC Code has only one area for coding anatomical structures, as indicated in the preceding paragraph, the anatomy fields (H-1, H-2, and I) must serve both Fields E and J. The relationships, however, are not difficult to understand: Whenever an organism is coded in Field J (indicated by any Field J symbol other than those beginning with letters S through Z), the entry in Field H must be a structure of the host coded in Field J. When Field J is not coded, or is coded with only a culture medium or environment (indicated by any Field J symbol beginning with letters S through Z), the entry in Field H must be a structure of the test organism coded in Field E.

Frequently, a test involves two types of information (and occasionally more than two) which concern anatomical structures, both of which are significant. It is for this reason that two fields have been provided instead of a single one. The types of information coded in Fields H-1 and H-2, the distinction between the use of Fields H-1 and H-2, and the relationship between these two fields (H-1 and H-2) and other fields (E, G, J, L, S, and T) are indicated briefly in the following paragraphs.

There are four general uses for Fields H-1 and H-2:

1. To record the gross anatomical structure or system responding to the compound or the structure or system in which the response is measured, this structure or system being of the test organism or of the host, as explained above in the second paragraph of this section. This first use represents the primary purpose for a coding provision for anatomy. FOR THIS PURPOSE, ONLY FIELD H-1 IS USED.

The remaining three uses of Fields H-1 and H-2 are for aspects other than specific responses of organs or systems to the test compound.

2. To record a gross anatomical structure or system which has been experimentally modified (chemically, surgically, etc.) prior to treatment with the test compound. Such modification may be made on either the test organism (coded in Field E) or on the host organism (coded in Field J) and the specific modification is indicated in Field G (for a test organism) or L (for a host organism).

When the experimental state coded in Field G or L refers to an anatomical structure that has been modified, the definition of the Field G symbol or Field L symbol in the Code includes the reference to Field H-1, H-2, or I. Therefore, if the experimental modification was to the organ specifically responding to the test compound or the organ in which the test response is measured (see Use Number 1 above), only a Field G or Field L entry can be used which refers to Field H-1. This is always indicated in the Field G or Field L definition (e.g., Symbol N of Field G: organ studied [specified in Field H-1] in a pathological state...). Similarly, if the modification is made to an organ other than the organ specifically responding, the Field G or Field L entry refers to Field H-2 and the Field G or Field L definition always directs the coder to make the entry in Field H-2 (e.g., Symbol Ø of Field G: organ [specified in Field H-2] in a pathological state).

3. To record the gross anatomical structure or system to which the test compound was applied. Field H-2 is used to supplement the description of the route of administration (coded in Field S-3), when the route of administration is not to the organ specifically responding (in Field H-1) and when the symbol used in Field S-3 can not adequately specify the organ or body area to which application was made. See Division 2 of Specific Directions and Explanations.

4. To record the gross anatomical structure or system which is the site of the tumor or pathological condition coded in Field E (Field H-1, rarely Field H-2). When Field J is coded with an organism

that is host to a tumor, noninfectious pathological condition, or parasitic organism, the anatomical entries of Fields H-1, H-2, and 1 always are structures of that host. (This was explained above in the second paragraph of this Section on General Use.) THIS SITE OF A TUMOR OR PATHOLOGY IS ALWAYS CODED IN FIELD H-1, with certain exceptions for special infrequently occurring situations explained in Division 6 of the section on Specific Directions and Explanations below. (Even for such an exception, however, when the site of a pathology is by necessity entered in Field H-2 instead of Field H-1, the fact of the transfer of the entry to Field H-2 is always clearly indicated in Field H-1 by the Symbol * [the IBM 12 zone punch] being used in Column 30.)

Specific Directions and Explanations

1. Distinction between uses of Fields H-1 and H-2

This is discussed in the previous section on General Use. In summary, Field H-1 is used for recording the primary organ, i.e., (1) the organ actually treated and acted upon by the test compound or the organ in which the test observation for response was made, or (2) the organ in which a tumor, non-infectious pathology, or parasitic organism was experimentally treated. Field H-2 is used to record organs other than the primary organ: (1) an organ other than the primary organ, specially modified; (2) an organ, other than the primary organ, to which the test compound was applied (when application was not directly to the primary organ), or (3) (rarely, and with an asterisk coded in Column 30 of Field H-1) an organ in which a pathology was treated (coded in Field E), when the response and observation was actually on an organ other than the organ most specifically affected by the pathology (see the example given in the last paragraph of Division 6 below).

2. Use of Field H-2 to supplement coding in Field S-3; a specific organ or body area at which application is made when it is not the responding organ or body area in Field H-1

In Field S-3 is coded the route of administration of a test compound. The descriptions of these routes often include designations of a specific anatomical structure to which or through which application is made. However, certain routes, as defined in Field S-3, are somewhat general, without specifying a structure (e.g., intravascular, or in an exposed organ, or topical, etc.--without specifying which blood vessel, organ, body area, etc., is actually treated). Since the specific organ or body area to which application is made is sometimes significant and indicated by the author, Field H is used with Field S-3 for coding it. If the administration (described in Field S-3) is directly to the organ which is the responding organ (in Field H-1), the responding organ and the organ to which application is made are identical and are both indicated by the identical entry in Field H-1. However, if administration is applied at a site other than the responding organ in Field H-1, this difference between the application site and the site of response must be recorded in Field S-3, both by code and by a written abstract. In coding this difference, it is necessary to supplement Field S-3 by designating a site of application (other than the responding organ in Field H-1) more specifically than the Field S-3 symbol is capable of doing, and for this Field H-2 is used. Field H-2 is used to supplement the following symbols of Field S-3: 3, 4, 5, 7, 8, B, C, D, E, F, G, I, Ø, P, S, and Z. None of the other symbols (0, 1, 2, 6, 9, A, H, J, K, L, M, N, Q, R, T, U, V, W, X, and Y) need to be supplemented by coding in Field H-2.

The following division explains how an entry in Field H-2 must be coded and subsequently interpreted relative to Field S-3 and Fields G-1 and G-2 and L. It also explains that there would be some advantage to having a special field for supplementing coding of Field S-3, since Field H-2 can only be used for this purpose when it is not occupied with organs related to coding in Field G or L or Column 30 of Field H-1. The latter coding areas must be examined before it can be certain that coding in Field H-2 relates to Field S-3.

3. Conflicts in Field H-2 due to its multiple uses; order of preference in use

The fields most especially related to Field H-2 may be regarded as two groups, (1) Fields G-1, G-2, and L, and (2) Field S-3, whose relationships to Field H-2 represent two distinct uses for Field H-2. There would be advantages in having three fields, each comparable to Field H-2--one for organs specially modified (Fields G-1, G-2, and L) and one for organs to which the test compound was

administered (Field S-3)--and a third for a site of a pathology coded in Field E when an organ other than that specific pathology site (yet affected by the pathology) is the organ responding to the test compound. However, the advantages of this were far outbalanced by advantages of restricting coding to a single IBM punched card, which did not permit more than the single Field H-2--used for all purposes. Unfortunately, as a result, any entry in Field H-2, considered as an isolated entry, is subject to any of three interpretations and therefore the meaning of any entry in Field H-2 can only be learned by consulting Column 30, Field G and Field L, and Field S-3 (in that sequence), explained as follows.

If an organ in Field H-2 is the site of a pathology coded in Field E, an asterisk will be in Column 30. (An explanation of the use of the asterisk and its importance is in Division 6.) If the organ in Field H-2 is in a special experimental state, Field G (or Field L) will be coded with one of the following symbols: Ø or P (or, less frequently, with S or T). If it is a specific organ to which the test compound was directly administered, Field S-3 will be coded with one of the following symbols: 3, 4, 5, 7, 8, B, C, D, E, F, G, I, Ø, P, S, or Z.

As might be expected, an occasional experimental design will present a conflict in Field H-2 which the CBCC resolves by observing the following coding procedure:

A. If a pathology coded in Field E is specifically of an organ other than the organ in Field H-1, an asterisk is coded in Column 30 and Field H-2 must be used only for coding the site of the pathology.

B. If Field H-2 is not used for the special (and infrequent) purpose of A, above, and any of Symbols Ø, P, S, or T are coded in Field G-1 or G-2, Field H-2 is used only for coding organs in the experimental states designated by these Field G symbols.

C. If Field H-2 is not used for purposes A or B, above, it can be used with Field S-3 to code organs (other than the organ in Field H-1) to which the test compound is administered.

This means that, in interpreting an entry in Field H-2, if an asterisk is coded in Column 30 (i.e., a 12 zone punch in Column 30), any entry in Field H-2 represents the site of the pathology, regardless of what is coded in Field G-1, G-2, L, or S-3. If Field G or Field L is coded with any of Symbols Ø, P, S, or T (and there is no 12 zone punch in Column 30), an entry in Field H-2 is always an organ related to that special state coded in Field G or Field L. If Field G or Field L is not coded with any of Symbols Ø, P, S, or T (and no 12 zone punch in Column 30), an entry in Field H-2 is always an organ to which the test compound was administered.

4. Relationship between the anatomy coding (Fields H-1, H-2, and I) and Fields E (test organism, pathology, or tumor) and J (host organism)

In the previous section, General Use, the four general uses of Fields H-1 and H-2 are explained. Regardless of which of these four types of information is coded, there is the further matter of understanding the correct coding correlation to one or the other of the test organism and the host, since there is only one area for coding anatomical structures and there are two places where organisms are coded.

If Field J is not coded (i.e., if there is no host), any coding of anatomy (Fields H-1, H-2, and I) necessarily concerns only structures of the test organism. If there is a host organism, the anatomy fields always are used only to name structures of that host coded in Field J. However, Field J may be coded with non-living "hosts" (culture media, environments, etc.); since the anatomy fields have no use relative to Field J in such cases, they may be used to code structures of the test organism coded in Field E. (In Field J, non-living hosts have code symbols whose beginning units are restricted to letters S through Z--i.e., symbols distinguished by beginning units which are indicated on the IBM punched card by combining numerical punches with the 0 zone punch.)

In summary: When Field J is not coded, all coding in Fields H-1, H-2, and I designates structures of the test organism in Field E. When Field J is coded with a host organism (symbols beginning with any letter other than S through Z--i.e., without the 0 zone punch in Column 37), all coding in Fields H-1, H-2, and I designates structures of the host organism. When Field J is coded

with a non-living host (symbols beginning with any of letters S through Z--i.e., with the 0 zone punch in Column 37), all coding in Fields H-1, H-2, and I designates structures of the test organism in Field E.

5. Relationship between the coding of anatomy (Fields H-1, H-2, and I) and the anatomical designations of TUMOR symbols (Field E)

Since the anatomy fields (H-1, H-2, and I) are used basically to record the anatomical site of action of the test compound, they are used for coding the anatomical site of any tumor that is treated in testing for carcinostatic or carcinogenic action. Although the tumor symbol bears a code designation of the anatomical site of origin (when the organ origin is known), this site of origin is not always the site of the tumor's location when chemically treated. Most frequently, the common experimental animal tumors used for testing candidate carcinostatic drugs are transplantable and, for technical convenience, such a tumor is ordinarily implanted in an organ and tissue other than the organ or tissue in which it originated. Thus, organs and tissues of tumor origin (Field E) and organs and tissues of locations of tumors when treated (Fields H and I) can both be indicated by code. In order to permit efficient sorting in Field H, the anatomical site of a tumor is always coded in Field H-1 when known, even when it duplicates the anatomical coding in Field E, as in the case of treatment of spontaneous tumors or tumors transplanted to other animals but at the same site as the tumor's origin. In retrieving information on all tumors having a specific anatomical origin, regardless of their location when treated, Field E must be searched. In retrieving information on all tumors in any given location, regardless of their origins, Field H-1 must be searched.

As can be seen by reference to the description of the Tumor Code, the symbols for organs and tissues incorporated into tumor symbols for Field E are not symbols of Fields H and I, but are derived from a special list of structures for the Tumor Code.

The site of an induced tumor is always coded in Fields H-1 and I when this information is known.

When a compound is tested specifically for its effect on metastasis of a tumor (Symbol 46 of Field T-2), the data frequently indicate all the organs to which metastasis has extended. When Symbol 46 is coded in Field T-2, only one code line is prepared with the organ of origin coded in Field H-1. However, if the effect of a test compound is on a tumor which has metastasized from another site and the effect is not specifically on the process of metastasis (i.e., when Field T-2 is not coded with Symbol 46), Field H-1 is coded with the site of the affected tumor (not the organ of origin) and Field F is coded with Symbol Y.

6. Relationship between the coding of anatomy (Fields H-1, H-2, and I) and the anatomical designation of PATHOLOGY symbols (Field E)

Fields H and I are always used to indicate the site of action of the test compound. Therefore, when a pathological condition is coded in Field E, Fields H and I are used to code the structures specifically affected by the experimental chemical treatment, regardless of whether the pathology (1) may be located exclusively in that structure, (2) is located (in addition to being a pathology of the responding structure) in several organs, a whole system, or the entire organism, or (3) is located in another part and affects only secondarily the structure responding to the chemical treatment.

In the case of an infectious disease, the infecting organism is always coded in Field E, the host is coded in Field J, and the system, organ, or tissue, in which is located the infecting organism, is coded in Fields H and I. Similarly, a non-infectious disease is indicated by a special symbol coded in Field E and the system, organ, or tissue in which is located the condition responding to the chemical treatment is coded in Fields H and I.

Non-infectious pathological conditions (e.g., coronary sclerosis), recognized and named as specific diseases, are frequently restricted by their definitions to particular anatomical systems, organs, or tissues. When this is the case, the Field E symbol for the pathology includes a designation of that anatomical structure involved (e.g., T32DP200 indicates, by -32D---- that the disease is specifically of the coronary artery). This permits Field H to be used for "modifying" the coding of the system or organ indicated in the pathology symbol--i.e., to specify a structure of that part indicated in the pathology symbol, or the more gross system or organ of which the structure indicated in

the pathology symbol is a part. (If the myocardium, or some other part of the heart, is affected by the test compound when treatment is given for arteriosclerosis or if some particular part of the vascular wall is affected, those responding parts may be indicated in Field H.)

Description of a given pathology condition is often very complex and the coding is necessarily difficult. As a result, the retrieval of information is not as simple as in the case of information on tumors or test organisms. To retrieve information on all diseases of a given anatomical structure, for example, not only must the anatomy Field H-1 be searched, but Field E should be searched for pathology symbols with anatomical components designating the particular structure.

Occasionally, the situation arises in which a test compound may have an effect on a disturbed organ which is itself not in the precise pathological state coded in Field E, although the organ exhibits pathology symptoms invariably associated with the condition coded in Field E. (An actual example encountered and coded was the experimental production of frostbite in a hamster leg which, when untreated, invariably caused a retarding of blood flow, as observed in peripheral vessels of the lining of the cheek pouch. Application of test compounds was specifically for treatment of the retarded blood flow [due to frostbite] observed in the cheek pouch.) In coding such data, that organ in which the test compound has its effect and on which test observations are made is coded in Field H-1 and the organ which is in the pathological state indicated in Field E is coded in Field H-2. To indicate that the organ in the pathological state coded in Field E is coded in Field H-2 rather than Field H-1, an asterisk (representing the IBM 12 zone punch) is coded in Column 30 of Field H-1. (Thus, for the example given above, "frostbite", Symbol TB003100, would be coded in Field E, "leg" [which would ordinarily be coded in Field H-1 as the location of the frostbite] would be coded in Field H-2, with an asterisk in Column 30, and "parietal blood vessel" would be in Field H-1 as the structure responding to the test compound.) In coding the situation just described, if the specific site of administration of the test compound is at neither the organ with the specific pathology of Field E (in Field H-2) nor the organ responding to chemical treatment (in Field H-1), and it is not adequately indicated by the entry in Field S-3, code the two organs as directed; the site of administration will not be coded except in Field S-3 where the site of administration should be written in if it is not explicit by the coding of that field.

A diagram illustrating the relationships between Field H and the pathology symbols and a further discussion of these is to be found in the Field E section describing the Pathology Code.

7. Relationship between the anatomy coding (Fields H-1, H-2, and I) and the dosage fields (Fields M and N)

The relationships between the dosage fields and the anatomical structures coded in Fields H-1, H-2, and I are thoroughly discussed in Division 5 of the Specific Directions and Explanations section of Fields M and N and reference should be made to that section and division.

8. Procedure for coding data from tests using special anatomical preparations consisting of an end organ and attached nerve (e.g., muscle-nerve preparations)

A common experimental procedure involves the use of an effector end organ and the nerve supplying the organ, the two organs being intact relative to each other, though they may be isolated from the animal or in situ. Under normal conditions, a stimulus applied to the nerve leads to a measurable response of the effector organ. Of these, the more common examples are nerve-muscle preparations, though data from nerve-gland preparations may occur.

Use of such an experimental preparation may vary in its objective: (1) By appropriate technique, there may be demonstrated the transmission of impulse to the effector organ (muscle or gland) and subsequently the effect of test compounds on this neuro-effector organ impulse transmission; (2) on the other hand, the action of a test compound applied to the nerve-organ preparation may be expressed only as affecting in one direction or the other the normal response of the effector organ to stimulation by the nerve with no exact determination as to whether the chemical effect is on the nerve, on the effector organ, or on the neuro-effector transmission.

If the test results are demonstrated by the author actually to be in terms of effects on transmission of the impulse (see Number 1 of the previous paragraph), the coding should record this by using the appropriate impulse transmission term in Field T-2 (e.g., neuro-muscular transmission, Symbol 98). Field H-1 should be coded with Symbol 17 or, if the specific nerve-organ pair are

identified, with one of the 17- symbol series. In addition, if it is an isolated preparation, Field G should be coded with Symbol R.

When results of a test using a specific nerve-effector organ preparation are expressed only as altering from normal the response of the organ to stimulation of the nerve (see Number 2 of the second paragraph above), the coder can not arbitrarily assume that the effect is on any specific one of the following: transmission of the impulse from nerve to effector, or on the effector organ, or on the nerve. The coding pattern instead should state only what was demonstrated by the test--the alteration, by the test compound, of the normal action of the nerve on the organ. The correct entries in Fields T-2, H-1, and T-1, are as follows:

(I) Field T-2: The organ's activity or state normally regulated or caused by the nerve is indicated in Field T-2. For example, if the vagus-heart preparation is involved, Field T-2 is used to indicate the cardiac process normally affected by the vagus nerve, heart rate. The CBCC Code lacks a field for expressing the normal action of the nerve on the process or state coded in Field T-2, just as the action of a secondary compound can not be expressed. (Field T-1 is used only to express the action of a test compound.) In the present example, Field T-2 can be coded to indicate only the action of the heart (cardiac rate, Symbol C1); the action of the nerve on the heart action can only be, and must be, included in the written abstract portion of Field T-2. (An alternative to this procedure would be the provision of many more special Field T-2 symbols such as "decreased cardiac rate due to vagal inhibition", but it was believed this would represent an unnecessary complication to Field T-2. The other alternative would have been the provision of another coding field for indicating action of nerves and secondary compound, but lack of space on the IBM card decided against it.)

(II) Field H-1: The organ pair (nerve and effector) is coded in Field H-1. A special group of such pairs are in Field H-1 of the Code; when any experiment concerns a nerve and its effector organ not in the Code, such a combination must be added to the Code and assigned a symbol. (Note that if the test method provides for administration of the test compound so that only one member of the pair is exposed to the chemical, that nerve or effector organ is coded in Field H-2, with the symbol for the pair coded in Field H-1.) This entry in Field H-1 (any Field H symbol of the 17- series) lends a special interpretive significance to the entry in Field T-2, in the same way that any entry in Field D lends a particular meaning to Field T-2: any action (of the nerve or of the secondary compound) on the biological state or process coded in Field T-2 is not indicated by coding but is only in the written abstract of Field T-2. (See also the preceding paragraph on coding in Field T-2.)

(III) Field T-1: In Field T-1 will be coded the action of the test compound on the action of the nerve, as the latter is recorded in Field T-2. This is accomplished by Symbol D, E, F, or G of Field T-1.

Example: The test compound reduces vagal slowing of the heart when the nerve is stimulated (using an isolated vagus-heart preparation).

Field G	Field H-1	Field H-2	Field I	Field T-1	Field T-2
R (Isolated preparation)	171 (Vagus-heart)	-	-	E (Decreases inhibition, by the nerve [H-1], of the process [T-2])	C1 (Cardiac rate)

Written in Field T-2: cardiac rate (retarded by normal vagal stimulation).

9. Blood and its components (symbol series 33-), lymph (symbol series 35-), and reproductive cells (Symbols 81C and 82B), included with gross structures of Field H

Although most properly these structures are considered as tissue and cellular units of the organism, they are included in Field H for reasons explained in Division 2 of the section on Specific Directions and Explanations of Field 1.

10. Symbols available for additional items of Field H

In Column 30 (Field H-1), the IBM 12 zone punch (Symbol *) has been given a special meaning (see Division 6 above). Therefore, none of letters A through I may be used for the second unit (Column 30) of anatomy structures. If a special list were made for Field H-2, letters A through I might be used in Column 33, but the CBCC has found the nine numbers and 17 letters (J through Z) adequate for the second unit of the symbols and a special list for Field H-2 unnecessary. For additional systems of animals, Symbol 4 (Column 29) is available; for additional plant organ systems, Symbol R (Column 29) is available. Symbols T through Z are also available, if needed for animal or plant organ systems.

11. File of coded biology data on IBM punched cards arranged according to symbols for gross anatomical structures

The CBCC maintains a special IBM punched card file of all coded information in which a primary organ has been involved and for which Field H-1 has subsequently been coded. The file is arranged by Field H symbols so that all coded information on any given structure can be retrieved by simple manual removal from this file (e.g., all coded information on the nervous system, in toto, or on the cerebellum, the heart, or the carotid sinus, etc.).

No such file has been established for secondary organs (Field H-2).

12. Double coding in Field H

Double coding is not permitted in Field H-1 or H-2. When Column 30 of Field H-1 is coded with Symbol * plus any one of Symbols 1 through 9 and J through Z (representing essentially the coding of two information categories), two IBM cards are punched. On the first, both symbols of Column 30 are punched; the second card is punched to be identical to the first except that the punch in the 12 position is omitted from Column 30. In the IBM Punched Card File arranged according to entries in Field H-1, the second card is filed according to the symbol for the organ, but the first card is filed separately at the end of the file; in all the other IBM Punched Card Files, the two cards are filed together. So few instances of the use of Symbol * occur in Column 30, the number of duplicate cards for such code lines is negligible.

TISSUES, CELLS, AND FLUIDS

Organization

The list of histological and cytological anatomical structures is organized by natural groups and assigned two-unit symbols (two IBM columns). The first unit indicates the general type of tissue and the second indicates the specific tissue. For example, all symbols beginning with the digit 2 (Column 35) are connective tissues, while adipose connective tissue is specifically designated by the second unit, digit 6 (Column 36).

General Use

The terms listed in this field are to be used in conjunction with Field H-1 (primary organs), to permit specific description of finer anatomical structures responding to test compounds. Occasionally, a tissue from Field I may be used in absence of an entry in Field H-1, when the organ is not specified in the article or when the tissue is not restricted to a single organ system.

Field I is coded only to relate to Field H-1 and never to an organ in Field H-2.

When Field E is used to code a pathology or a tumor, Field I, as well as Field H-1, is used only to describe the anatomical location of the tumor or pathology.

Specific Directions and Explanations

1. Use of terms of Field I which are identical to terms of Field H

Several terms occur in both Field H and Field I, due to anatomical complexity. For example, most organs are supplied with blood vessels and nerves, each of which can be considered themselves as organs. These structures which can be anatomical parts of more gross organs are included in Field I as well as Field H. Thus, when blood vessels of a specific organ are affected, it is possible to code the particular vessels by combined use of Fields H-1 and I. On the other hand, if blood vessels are generally affected, regardless of their relationship to specific organs, they can be coded in Field H-1 as the organ affected. The following examples demonstrate the foregoing.

Example 1. The test compound caused inflammation of arterial walls as evidenced by observations on the femoral artery.

Field T-1	Field T-2	Field H-1
7	1132	325
(produces)	(inflammation)	(of the arteries)

Example 2. In studying factors which affect the kidney blood flow, the test compound was found to produce inflammation of the nephric (kidney) blood vessels.

Field T-1	Field T-2	Field H-1	Field I
7	1132	71	C1
(produces)	(inflammation)	(of the kidney)	(blood vessels)

2. Certain tissues included in Field H as organs: blood, lymph, and reproductive cells

While blood is commonly considered as a specific tissue, the collective blood mass can at the same time be justifiably regarded as an organ constructed of but a single tissue. Lymph might similarly be regarded as an organ. If either were coded in Field I, as a tissue responding to the test compound, there would seldom be anything of significance (i. e., only "blood vessel" or "body as a whole") needed

in Field H, although to imply by such coding that a blood vessel or the body as a whole is affected because the fluid it contains is affected would be inaccurate. Therefore, blood and lymph are coded in Field H and are not included among the Field I items as tissues. There has been no occasion when "blood" has been needed in Field I to specify a tissue of a particular organ coded in Field H-1. I. e., "arterial blood", "venous blood", "renal blood", "cerebral blood", etc., have not been distinctions the CBCC has found a necessity to make. However, if this is necessary, these particular designations can be added to Field H with new symbols of the 33-series.

Sexual reproductive cells are confined to the two structures, ovary and testis, although, in the normal course of events, they are discharged from the ovary or are propelled from the testis to traverse paths through other structures. Therefore, though they are by nature cells (or germinal tissues) rather than organs, their being coded in Field I, with ovary or testis coded in Field H-1, most often would represent a redundancy (i. e., when sperm or ovum is coded, it may be assumed that they are in the testis or ovary or parts thereof). For this reason, the CBCC codes sperm and ovum in Field H, for the sake of expedience. If for some reason it becomes important to distinguish sperm of the seminiferous tubules from sperm of the epididymis, for example, the Code may be modified by adding new specific items to Field H (seminiferous tubule sperm, vasa efferential sperm, epididymal sperm, etc.) or by adding sperm (and ovum) to Field I.

3. Symbol 64; the test compound's effect on a product of a gland

When a normal component of a glandular product is increased or decreased in quantity by the test compound, the effect is coded with one of the FC-- symbol series in Field T-2, with Field T-1 Symbols 1, 2, 3, 4, or 5. However, there is no way of indicating by this coding in Field T-2 whether the component of the gland's secretion is produced in abnormal amounts due to merely altering the total volume of the gland's secretion or due to altering the relative composition of the secretion. Symbol 64 has been provided in Field I to distinguish these two effects of the test compound (though doubtless secretions are not ordinarily considered to be body fluids). The symbol indicates that the test compound affects that total secretory product (of the gland coded in Field H-1) in the manner indicated in Field T, by altering its basic character (i. e., by altering its composition relative to the component specifically coded by the Field T-2 symbol) rather than altering merely its volume. Therefore, when only volume of the total secretion has been altered, though the components of the secretion remain proportionately normal per unit volume, Symbol 64 must NOT be used in Field I.

4. Symbols available for additional items of Field I

None of the IBM zone punches have been assigned a special meaning in Field I. Therefore, there are no restrictions in use of any letters in either column for constructing symbols.

5. File of coded biology data on IBM punched cards arranged according to symbols for tissues and cells

The CBCC maintains a special IBM punched card file for all cards on which Field I has been coded, arranged according to Field I code symbols. Thus, all coded data in which a given tissue is affected by test compounds, or in which was located a pathology that is affected by test compounds, can be taken quickly and by manual selection from this file.

6. Double coding is not permitted in Field I.

FIELD J
Columns 37, 38, 39,
40, 41, and 42

HOST ORGANISM OR TEST ENVIRONMENT

Organization

The symbols of Field J have a maximum of six units corresponding to the six IBM columns used. As in the case of the code symbols for test organisms of Field E, symbols of Field J are constructed to indicate the taxonomic affinities of the host organism. Thus, Column 37 is used only for indicating phyla and the symbol for any given phylum or plant division is a single unit symbol of Column 37 (Protozoa, Symbol 1; Thallophyta, Symbol J, e.g.). Column 38 is used only for coding classes of each phylum (the symbol for any one class is a two unit symbol of Columns 37 and 38 [Sarcodina, Symbol 11; Ciliata, Symbol 12, e.g.]). Similarly, Column 39 is used for distinguishing orders of each class (Amoebozoa, Symbol 111; Foraminifera, Symbol 112, e.g.) and Column 40 distinguishes families (Meleagrididae, Symbol A611; Phasianidae, Symbol A612).

The phylum, class, and order designations of Field J (Columns 37, 38, and 39) are the same as those designations for test organisms in Field E (Columns 18, 19, and 20). This similarity has no coding significance; it was merely an expedience in constructing the Field J list subsequent to the construction of the taxonomy list for Field E. However, the similarity with Field E symbols ends with the designations of order; familial, generic, and specific units of Field J symbols are unique to Field J.

The family to which the host belongs is indicated by a single unit (the fourth unit, Column 40), in contrast to the familial designation of Field E which uses two units (two IBM columns). The families of Field J are merely assigned sequential fourth-unit symbols as they are added to the list under each order. Thus, of the order Carnivora, Canidae was the first family listed in Field J and was subsequently assigned Symbol A721, while the second family listed of this order, Felidae, was assigned Symbol A722, etc.

The final two units (Columns 41 and 42) are reserved for designation of specific members of the family, as well as for indicating particular varieties and strains. In other words, of the two final columns in the field, one has not been dedicated to coding the genus of a host and the other dedicated to coding the species of the genus. Instead, they are used together as a unit in which the host's genus and species names are coded as a single unit (e.g., Cricetus cricetus, Symbol ----01, Mesocricetus auratus, Symbol ----02, etc., of family Geomyidae, Symbol A733--). This is accomplished by the simple expedient of assigning sequential symbols to species or strains as they are added to the list, reserving blocks of symbols for further strains and varieties of a species when it is recognized that several strains exist and might be purposefully used in chemical tests. For example, of the family Canidae (Symbol A721), the first member listed was the dog, Canis domesticus, and this is assigned Symbol A72101 (defined as being an unspecified breed). Since there are many breeds of dogs and since it is probable that it will some time be of some importance to be able to code the breed distinction, a number of symbols are reserved for this purpose, A72102 through A7211Z, representing 69 symbols for 69 breeds. (Although no breeds have yet actually been entered in the list, the following possibilities are suggested as illustrations: Collie, A72102; German Shepherd, A72103; Doberman, A72104, etc.) The next species added was the wolf, Canis nubilis, to which is assigned the symbol A72121. Although it is improbable that Canis nubilis used as a host would be of a particular breed or variety, four symbols are nevertheless reserved for that possibility (A72122 through A72125). Thus, the next member of the list, the coyote, Canis latrans, is assigned symbol A72126 and four symbols reserved for coyote varieties (A72127 through A7212A).

Inasmuch as the two columns, as they are used, permit 1260 symbols for as many different species and strains of each family, it is probable that the scheme is adequate for all hosts used in chemical-biological tests.

Considering data from all chemical-biological testing, the organism species or forms used as hosts are many fewer than the number used as test organisms, largely because in many chemical-biological tests, a host plays no role (i.e., Field J is not used); further, most therapeutic testing involves infection of vertebrates and higher plants and little data may be expected from chemical tests in which an invertebrate or lower plant is the host (one exception being bacterial hosts of viruses).

For this reason, it has been unnecessary to use as much IBM space for as large a number of families, genera, and species in Field J as is necessary in Field E.

When an organism is used as a host in a chemical test, there is introduced an experimental factor that is frequently of critical importance, the relationship between the parasite and its host. For scientific control in a test, it is important that a living host be as carefully selected and standardized as a non-living host, whenever possible. To achieve maximum control, it is frequently not only a particular species that is selected as the parasite's host during the test, but a carefully selected, distinct strain of that species. Within a single species may be several strains which perform with great dissimilarity as hosts to a given parasite species. Not only may the interrelationships between parasite and the host vary according to the strain of the host into which the parasite is inoculated, but the response of the parasite to chemical treatment may vary with the host strain and the responses of different host strains to the test compound may vary. For this reason, Field J symbols have been endowed with strain (variety or breed) designations, as described above.

General Use

Field J is the area for coding the host of a test organism, when the test organism is in or on such a host. This host may be a living organism or it may be a non-living environment such as a specific culture medium, soil, stored food (flour and cereal, e.g.), water, etc., in or on which the test organism is resident when the test compound is applied.

A pathology coded in Field E, whether it is infectious (caused by a pathogenic test organism) or non-infectious, is accompanied by an entry in Field J describing the host of the pathogen or pathology. Likewise, a tumor coded in Field E is accompanied by an entry in Field J describing the living (or, occasionally, non-living) host of the tumor.

The host represents an important factor of chemical-biological tests, interposed as it most frequently is between the test compound and the object of the treatment in Field E (i.e., the test organism, pathology, or tumor). A test compound, administered as an experimental therapeutic is applied at a selected (and presumably optimal) site of the host which means that it is often applied only indirectly to the infecting organism, site of pathology, or tumor. Frequently, little is known about the details of the host's metabolic handling and rate or path of disposition of the chemical (i.e., the host's response to the treatment). Although this observation is made with living hosts particularly in mind, certain non-living host materials may represent unknown factors relative to the dilution/concentration/alteration of the test compound. Therefore, when a host is involved, the outcome of a test--i.e., the therapeutic evaluation of the test compound--must always be interpreted by regarding the host as an agent which possibly acts to dilute, concentrate, or chemically alter the test compound. Division 8, of the following section, explains how this is related to coding procedure.

Specific Directions and Explanations

1. An animal or plant PART, excised and maintained in a LIVING CONDITION, as a host; the bath or nutrient solution needed to maintain the excised part

Occasionally, for convenience in testing, a test organism is in or on an excised part of a host organism rather than in or on the intact host, the excised part being maintained in a living condition or so little altered by excision that its performance as a host is thereby representative of the condition in the intact, living host, in contrast to organs or tissues in which the protoplasmic contents are altered by actual death. (Examples of these "excised living" hosts are organ slices, tissue slices, tissue breis, or excised organs such as the liver, leaves, or fruits.) Since the results of such tests can reasonably be projected to the intact living organism as a host, Field J is coded with the symbol for the organism and Field L is coded with Symbol R (or Symbol T, as described below) to indicate that it was only a representative part of the host that was actually used in the test. The excised organ or tissue is coded in Field H-1 or I. (See also Division 4, below.)

If it is desirable to maintain this excised part of the host for any period of time, a nutrient solution or saline bath, etc. (i.e., a "secondary host") is frequently necessary. For this reason, a second coding area for this "secondary host" would appear useful. Because occasions have been so few when the CBCC needed a second coding field for such a secondary host, it has not been considered practical to reserve IBM punched card space for it. Therefore, having only one field for hosts, Field J is coded with the host organism donor of the excised part (as described in the previous paragraph), while the bath or nutrient solution (the "secondary host") can not be coded (except that sometimes coding in Field S-3 [Symbol C] implies the presence of a bath--when the test compound is applied in the bath). However, when an excised part used as a host (ordinarily indicated by Symbol R of Field L) is placed in a "secondary host", always code Field L with Symbol T. It is necessary to include in the written abstract for Field L the specific solution, bath, etc., which plays the role of secondary host.

2. Tumor hosts

The discussion and description of the Tumor Code of Field E includes an explanation of tumor hosts and the use of Field J. Regardless of the organism in which the tumor originated, the organism in which the tumor is located at the time of the chemical test is coded in Field J. Thus, for chemical tests using transplanted tumors, the species and strain of the organism into which the tumor was transplanted for the test is coded in Field J.

In accordance with this procedure, any non-living host (nutrient medium, saline bath, etc.) in which a tumor (or tumor slice, brei, etc.) is maintained during a chemical test is coded in Field J, regardless of the organism in which the tumor arose.

When a compound is tested to produce a tumor (i.e., tested for carcinogenicity), the coding of this action is accompanied with an entry in Field J which is always the organism in which the compound was tested.

3. Non-living materials: discrimination between their uses as HOSTS and as mere CONVEYERS OF THE TEST COMPOUND

Most often it is not difficult to distinguish between a non-living material which serves as a host to the test organism being treated and the other non-living materials or instruments used in the experiment. A non-living host is ordinarily a material on or in which the test organism normally is found, either permanently or occasionally, or it is a material which serves directly to nourish and sustain the test organism; in either case, the material is representative of the organism's normal environment, however artificial may be the nutrient or sustaining medium.

For example, in an experiment in which the test compound is a gas bubbled into an aquarium where algae are the test organisms, the host is the material constituting the normal intimate environment of the test organism--i.e., water; it is not the tube leading the gas to the water, nor the glass aquarium housing the algae and water. Again, in experiments in which the test compound is deposited on or in a material (glass, wood, cloth, etc.) which flies (as test organisms) are induced to contact or on which are placed lice (as test organisms), the glass, wood, cloth, etc., are properly regarded as hosts, since they were selected as representative of environmental surfaces which the test organism might normally contact. In an experiment in which a test compound mixed with an attractant is placed in a glass dish in a cage of flies, the glass can not be regarded as the host material but merely as the container of the test compound and attractant (in the same way as the tube of the aquatic experiment was only the conveyer of the test compound); in this situation there would be no entry in Field J.

In any experiment in which a volatile test compound is deposited on a material (or placed in an open container) and in which the chemical acts as a gas diffused through the air, the material or container on or in which the chemical is deposited is not a host, but merely a conveyer; the host is the treated air. Similarly, if a water-soluble compound is deposited on a material (glass or cloth, e.g.) which is subsequently immersed in water to treat aquatic organisms, the water is the host to be coded in Field J and the material on which the test compound was deposited is merely the conveyer.

A written record of the conveying materials and instruments should be included in Field J as well as the actual host materials.

4. Excised parts of plants and animals used as hosts; coding of these in Field J, as "LIVING" or "NON-LIVING", is dependent on their representation of the normal, intact condition

When an excised part of a plant or animal is used as a host, the code entry in Field J is sometimes the symbol for the organism from which the organ or tissue was taken. Sometimes, however, the organ or tissue is coded in Field J merely as a general plant or animal product such as "meat", "grain", "eggs", "wood", etc., unspecified as to the particular organism from which it came.

Which of these two possible Field J entries should be used in a given situation is determined by the condition of the excised structure used as the host organ or tissue. If it is maintained in a relatively normal "living" state, even though excised, it and its function as a host are considered to be reasonably representative of that organ or tissue in the living, intact organism. Under such conditions, the organism is identified by code in Field J and Field L is coded with Symbol R or T to indicate that the organ or tissue coded in Field H-1 or I is excised. This point was discussed also in Division 1, in explaining the coding of a bath or nutrient solution for such an excised host. (For the special problem of coding seeds and fruits as hosts, consult Division 5 below.)

In contrast to excised organs and tissues maintained in a state resembling that in the living, intact organism, there are those plant and animal organs and tissues, used as hosts, which have undergone death and the alterations characteristic thereto. (Although certain structures of the living, intact organism are dead, such as heartwood, hair, nails, etc., the coding problem under discussion concerns only excised structures which are of living tissues in the intact state.) When an excised plant or animal part is dead, it no longer is strictly comparable to the same organ or tissue when it is a living part of the intact organism, neither in response to the organism that would use it as a host nor in response to the chemical administered. Because it is not representative of the organ or tissue of a living, intact organism, it is coded for what it is, an animal or plant product, such as meat, fur, leather, eggs (dead), wood, straw, fiber, etc. (symbol series V- and W- of Field J). In this case, Fields K and L are not coded. Neither are Fields H-1 and I coded when Field J is coded with any of the symbol series V- or W-, unless a particular organ or tissue of the test organism responds specifically to the test compound, in which case Fields H-1 and I are considered available for coding that organ or tissue.

When a host organism, coded in Field J, is used in one of the special experimental states, homogenate, extract, culture, or slice, Field L is coded to indicate this state. This preparation is not considered to be non-living and coding the organism in Field J, in one of these four states indicated in Field L, implies its living state (otherwise, Field J would be coded with one of the non-living hosts, symbol series S- through Z-). In this situation, the coder must never use the Field T-2 symbol series 18- to code the test compound's action because those symbols are used only to describe the effect of the test compound on the test organism's development on non-living hosts.

5. Excised and stored FRUITS and SEEDS as hosts are identified as such by being described in Field K as the STAGE of the plant coded in Field J--OR--are coded in Field J as a general plant product, according to their STATE. (See also Division 6.)

Fruits and seeds, in particular, cause confusion in interpreting them as hosts, making necessary this explanation of the CBCC procedure relative to coding them. The confusion is due partly to their unique nature; they are living organs of the plant, predestined to be discarded by the plant, yet some part of the organ remains alive long after the organism has discarded it, the most persistent being the new, embryonic individual in the seed. When these discarded living organs are used as hosts, it is a question of knowing at what point to cease regarding them as living organs of a specific organism and when to consider them as merely a non-living plant product. Although the CBCC decision has been somewhat arbitrary, the following procedure should always be observed for sake of consistency.

In the case of undehydrated fruits having fleshy parts (apples, tomatoes, bananas, oranges, etc.) and in the case of seeds in the undehydrated condition (green beans, peas, sweet-corn, etc.), in other words, in the case of fruit and seeds in the same general condition they were in as living organs on the intact plant, they are considered as living organs of the plant, since chemical treatment of excised fruit in the condition described is conceivably comparable to such treatment before excision when there is no question about their being considered as organs of the plant. Thus, the plant is identified by code in Field J, Field L is coded with Symbol R and the fruit or seed is coded in Field H-1. Field K is coded with "fruiting plant", Symbol 8.

When the seed or fleshy part of the fruit has dehydrated (prunes, dried apricots, dried peanuts, dried corn and beans, etc., including seeds and fruits which dry before removal from the plant) even though they may contain still living embryos, the CBCC has regarded them, for coding purposes, as being sufficiently altered from the living organ of the plant to be coded as a non-living host, i.e., a plant "material". Thus, wheat, oats, corn, beans, peanuts, etc., which have been dried sufficiently for successful storage are coded as non-living hosts (symbol series V- of Field J) when a test compound is applied to them to protect them from test organisms. In this case, Fields K, L, H-1, and I are not coded, except that Fields H-1 and I are available for coding structures of the test organism.

6. Living seeds (or fruits containing living seeds), treated to affect a test organism on the EMBRYOS

In general, coding of stored seeds and fruits as hosts is according to the procedure described in Division 5 above. However, if the treatment is made to the seed or fruit when the host structure is precisely the living, dormant or germinating embryo or young seedling in or on which is (or will be) the test organism, the treatment is considered as being to the young, living plant and the symbol for the plant should be coded in Field J (rather than the symbol for the plant seed or fruit), regardless of whether the seed or fruit is dehydrated; Field K should be coded with the stage treated (embryo), Field L should not be coded, Field H-1 will be coded with "embryo unspecified" (or with the embryonic part on which is the test organism), and Field H-2 will be coded with the external coat of the seed or fruit on which the chemical application was made.

7. The material in which a plant, as a TEST ORGANISM, is rooted is not necessarily coded as the plant's host

When a plant is the test organism and it is growing in ordinary, suitable soil, and when application of the test compound is directly to the aerial part of the plant, the soil is not a significantly variable factor of the test any more than is the air surrounding the plant. Therefore, neither soil nor air need be coded in Field J in this situation; i.e., Field J will not be used.

However, if the test compound is applied to the soil, rather than directly to the plant, the soil assumes an important role in the test and must be coded in Field J as the environmental "host" material through which the test organism receives the test compound.

If a series of chemical tests are performed on plants which differ only in being potted in soil variants (sand, clay, loam, e.g.) and the chemical is applied only to the aerial portion in each test, the soil assumes an importance that it does not have when only one soil type is used (which may be assumed to be the preferred soil for the plant). In the code line for each test of such a series, the soil type should be coded in Field J, even though the chemical application is not made to it. (For this situation in which Field J is coded, yet application of the test compound is directly to the test organism, note carefully the coding of Fields M and N, as explained in Division 8 below.)

When plants are grown in a medium in which they are not naturally found growing (i.e., an artificial medium such as a nutrient solution, perlite, vermiculite, etc., or a soil or water to which they are essentially alien), that medium is coded in Field J as the host, even when the test compound is not applied to it but directly to the test organism. (Note carefully the coding of Fields M and N in these situations, as described in Division 8, below.)

8. Relationship between Field J and the dosage fields, M and N

When Field J is coded, it is assumed that the dosage recorded in Fields M and N is the dosage administered to that host, by the route indicated in Field S-3. Any exception to this must be indicated by code in Fields M and/or N, according to whether one or both are coded. Thus, when the dose in Fields M and N is the dose to which the test organism (or tumor) is directly exposed, any entry in Field J must be accompanied by a symbol designating that the entry in Fields M and N is not the dose the host receives but is the dose to which the test organism or tumor is exposed; this distinguishing symbol is the IBM 11 zone punch in Columns 45 and/or 47 of Fields M and N (coded as Symbol #). If there should be determined the concentration to which was exposed a responding organ or tissue of a test organism in a host, this would be indicated by using the 0 zone punch in Columns 45 and/or 47 (coded as Symbol 0).

The 11 or 0 zone punch in Fields M and N, then, is interpreted as indicating that, in spite of an entry in Field J, the dose coded is the dose administered directly to the test organism or an organ of the test organism of Field E or that it is the concentration of the test compound in the host to which the test organism is exposed, as determined by analysis of the host some time after administration to the host. In other words, the 11 or 0 zone punch indicates that the coded dose is not the dose (concentration or quantity) administered to the host coded in Field J. (This is explained also in Fields M and N, Specific Directions and Explanations section, Divisions 5, 6, and 8.)

9. Relationship between Field J and the anatomy fields, H-1, H-2, and I

When Field J is coded with a host organism, Fields H-1, H-2, and I are used only to code organs and tissues of that host organism. However, when Field J is coded with a non-living host (a nutrient medium, bath, etc.), the anatomy fields are used only for coding parts of organs and tissues of the test organism.

Symbols for non-living hosts all begin with letters recorded on the IBM punched card by using the 0 zone punch (letters S through Z). Therefore, when Field J is coded with a symbol beginning with any of letters S through Z (i.e., if it is punched with the 0 zone punch in Column 37), any entry in Field H-1, H-2, or I represents anatomical parts of the test organism in Field E. When Field J is coded with a symbol beginning with any number or any letter A through R (i.e., if it is not punched with the 0 zone punch in Column 37), any entry in Field H-1, H-2, or I represents anatomical parts of the host organism in Field J.

10. Relationship between Field J and Fields K and L

Rather than use a single coding area for coding special experimental conditions and sex and stage of the test organism (when no host organism is involved in the test) or of the host organism (when a host is involved), the CBCC has found it necessary to have two such areas. Thus, Fields F and G represent the coding area used only for sex and stage and special experimental conditions of the test organism, whether or not the test organism is in a host. The two fields, K and L, describe the sex and stage and special experimental condition of any host and if no host is coded, Fields K and L are unused.

11. Variations of standard nutrient media and solutions

Among the non-living hosts are listed a number of standard nutrient media or saline solutions (e.g., Ringer's solution and Tyrode's solution). Occasionally, one of these will be altered slightly for some experimental reason and will be reported thus (e.g., "potassium-free Tyrode's solution"). Instead of assigning a unique symbol to each of these many variants of a standard medium or solution, the CBCC uses the symbol for the standard solution and explains the deviation from the standard on the Code Sheet in the written abstract portion for Field J.

12. Definition of "culture medium"; use and significance of symbols of the X--- series

Symbols of the X--- series (of the group of non-living hosts, S--- through Z---) are defined as "media" and, as such, refer to laboratory-prepared mixtures of known composition which have been determined to be adequate for satisfying the test organism's requirements for life, growth, and reproduction. It is possible that a completely adequate culture medium may consist merely of one of the specific natural materials coded by Symbols S--- through W--- and Y--- and Z---. For example, a sugar solution (Symbol T6) or cheese (Symbol W51) may be entirely adequate as a culture medium for growth of an organism (e.g., a given mold) to be tested for response to a test compound; the natural materials (e.g., yeast concentrates, eggs, flour, cheese, etc.), however, lack the degree of standardization that is possible with artificially prepared mixtures.

The symbols of series X--- in Field J are not necessarily conceived as making distinction between inadequacy and adequacy of a non-living host (i.e., while items coded with symbols of series X--- are assumed to be adequate for the test organism, items coded with other symbols are not assumed to be inadequate for the organism being grown in or on it), nor to make an absolute distinction between the artificiality or naturalness of the non-living host, nor between the standardization or non-standardization of the non-living host. Symbols of the X--- series pretend a function no broader

than to code literally those specific artificial media when used in a test or when the substrate of the microorganism is described merely as "culture medium".

13. Code symbols of Field J having less than six units

An author may occasionally identify a host only as to family, for example, for which reason only the symbol for the family would be used. Since this symbol has only four units, Columns 41 and 42 would be left uncoded. The CBCC has established the practice of cross-hatching any final unused "code boxes" of Field J on the Code Sheet when the entry is identified only as to family, order, class, or phylum; this is merely to assure the operator punching the IBM card that the short symbol of Field J is deliberate and that the unfilled code boxes do not represent unfinished coding.

14. Symbols available for additional items of Field J

Zone punches have not been assigned special meanings in any of the Field J columns. Thus, there are no restrictions on use of any symbol in any column for constructing host symbols.

The last animal symbol of the present list begins with the letter G and the first plant symbol begins with the letter J. Similarly, the last plant symbol begins with the letter M and the first non-living host symbol begins with the letter S. The letters H and I and N through R in Column 37 are available for expansion of animal hosts (H and I) and plant hosts (N through R). By restricting animal hosts to symbols beginning with 1 through 9 and A through I, plant hosts to symbols beginning with J through R, and non-living hosts to symbols beginning with S through Z, it permits all plant hosts to be recognized (and retrieved) by the IBM 11 zone punch and all non-living hosts to be recognized (and retrieved) by the IBM 0 zone punch.

15. File of coded biology data on IBM punched cards arranged according to symbols for hosts

The CBCC maintains a separate IBM punched card file of all the coded chemical-biological data in which a host plays a role, i.e., all cards on which Field J is punched. This file is arranged according to the sequence of Field J symbols. Therefore, in searching for all information concerning a specific organism (or non-living host, for that matter) that has been used as a host (e.g., all information concerning a specific organism that has been experimentally treated for diseases), the CBCC can quickly retrieve it from this field by a single manual action.

16. Double coding of hosts in Field J prohibited

Since CBCC coding procedure is dependent on IBM punching methods, two hosts are never coded in a single code line. If all aspects of two tests are so similar that the coding of the two would be the same for all coding fields except that different hosts were used, the two tests could not be recorded in a single line by coding both test organisms in Field J; a separate line is necessary for each host.

SEX AND STAGE OF DEVELOPMENT OF THE HOST ORGANISM

The organization, general use, and, for the most part, the specific directions and explanations for Field K are so nearly like those for Field F that repetition is unnecessary. Keeping in mind that coding in Field K describes the host in Field J, the discussions of Field F (describing the test organism in Field E) can be interpreted to apply to Field K. It will be noted that any reference to Symbols S through Z does not apply to Field K, for which reason none of Division 5 of the Specific Directions and Explanations for Field F is applicable to Field K.

As in the case of Field F, the CBCC maintains no file of coded data (IBM punched cards) arranged by code entries in Field K.

Double coding is permitted in Field K, just as double coding is permitted in Field F as described in Division 4 of Field F.

PRETREATMENT OR
EXPERIMENTAL STATE OF THE
HOST ORGANISM OR OF THE ORGAN,
TISSUE, OR CELL (OF THE HOST ORGANISM)
WHICH IS THE SITE OF THE
PARASITE, NON-INFECTIOUS PATHOLOGY,
OR TUMOR CODED IN FIELD E

Symbol Z only:
EXPERIMENTAL TREATMENT OF THE
HOST OTHER THAN TREATMENT
WITH THE TEST COMPOUND
AND COMPOUND CODED IN FIELD D

Note: The organization, general use, and specific directions and explanations for Field L are so similar to those for Field G that a complete account would be largely a copy of that for Field G. To avoid total repetition, the coder is requested to refer to the explanation of Field G, applying that explanation to Field L. The following description of Field L, therefore, is principally to distinguish its use and its relationships to Fields J, H-1, H-2, and I from the use of Field G and its relationships to Fields E, H-1, H-2, and I.

Organization

Most of the items of Field L are almost identical in definition and organization to those of Field G. The coder is referred to the explanation of the organization of Field G. However, in coding Field L, reference should be made only to the definitions of symbols in the Code section for Field L.

General Use

Field L is used only to code experimental states of a HOST organism coded in Field J. Since the relationships of Field L to Field J are so nearly identical to the relationships of Field G to Field E, the coder is referred to the explanation of the general use of Field G. In that discussion, references to "Field G", "Field E", "test organism", "test organism's organ or tissue", and "organ or tissue responding to the test compound" can in general be translated to "Field L", "Field J", "host organism", "host's organ or tissue", and "organ or tissue site of the pathology in Field E", respectively, in order to apply the explanation to Field L. The following corresponds to the four divisions of the explanation of the general use of Field G.

1. Field L. (Read Division 1 of the General Use of Field G, applying that discussion to Field L.)

2. Field L is a single column coding area, in contrast to Field G which is divided into two coding areas, G-1 and G-2

For practical reasons, less coding space has been awarded to coding pretreatments and experimental states of host organisms than for coding pretreatments and states of test organisms. While it is true that occasionally a single coding area (Field L) is inadequate for coding all experimental states of a host, just as two areas (Fields G-1 and G-2) are sometimes inadequate for coding all states of a test organism, the infrequency of need for more than one Field L justifies the CBCC's reserving only one IBM column for it.

3. Relationship of Field L to Fields J, H-1, H-2, and I. (Read the first two sentences of Division 3 of the section describing General Use of Field G, applying that discussion to Field L and Field J.)

The latter part of Division 3 of the General Use section of Field G can not be interpreted strictly to relate to Field L for the following reason. Although the relationships between Field L and Fields H-1,

H-2, and I are essentially the same as between Field G and Fields H-1, H-2, and I, the definition of anatomical entries in Fields H-1, H-2, and I varies, depending on the coding in Field J: when a living host is coded in Field J, Fields H-1, H-2, and I are used to code anatomical sites of the pathology in Field E (i. e., anatomical parts of the host), rather than anatomical parts which respond specifically to the test compound (i. e., rather than anatomical parts of the entry in Field E).

4. Significance of information about experimental states coded in Field L. (Read Division 4 of the General Use of Field G, applying that discussion to Field L.)

Specific Directions and Explanations

Note: In the following, reference need be made to the corresponding division of specific directions and explanations for Field G ONLY when it is suggested to do so.

1. Field L is related exclusively to Field J and to Fields H-1, H-2, and I THROUGH Field J

2. Coding when presence of a tumor in the host is incidental

When a host has a spontaneous tumor and the information being coded is unrelated to any response of that tumor to the test compound, the tumor's presence is incidental and should be coded in Field L with Symbol 7, N, or Ø, not with Symbol 5. (If the incidental tumor is not spontaneous, but implanted, use Symbol S.)

3. More than one experimental state of the host

If more than one experimental state characterizes the host, only one can be coded (whichever is the more significant, if a choice is possible). The other states must be described in the written abstract portion of the field.

4. Relationship of Field L to Fields J, H-1, H-2, and I

Field H-2:

When Field J is coded with a host organism (any Field J symbols beginning with any of numbers 1 through 9 or letters A through R), Fields H-1 and I are used only for coding the anatomical site of the pathogen, non-infectious pathology, or tumor coded in Field E. Field H-2 is used to code any organ other than the specific anatomical site of the pathology: an organ to which the test compound is administered (when it is not administered to the organ in Field H-1), for example, or an organ (other than the organ in Field H-1) which is given special pretreatment or is in a special state as indicated by any of certain entries in Field L. (See Division 5 below for a more complete explanation of the uses for Field H-2.) The point to be made here is that Field H-2 can be used with Symbol B, Ø, P, or S of Field L to describe those experimental states of the host organism in Field J.

Fields J, H-1, and I:

When Field J is coded with a host ORGANISM (which is the only occasion when Fields H-1, H-2, or I relate directly to Field J rather than Field E), rather than a non-living host, Field L is used to describe a state of the host organism as a whole (Field J), or of the anatomical site of the pathology in Field E (Field H-1 or I). Certain of the items of Field L have an ambiguity of reference to Fields J, H-1, and I. (This is true also of items of Field G in their relationships to Fields E, H-1, and I and it is discussed under Specific Directions and Explanations for Field G, Division 4. The coder should review that explanation.) Except for items coded by Symbols 5, 7, 9, A, F, G, H, I, K, L, Ø, and P which include in their definitions specific reference to Field J or H, reference must be made to the written abstract of the Code Sheet to ascertain that the pretreatment (or experimental state) coded in Field L was of the host organism as a whole in Field J, or particularly of the organ in Field H-1, or of the tissue or cell in Field I. Actually, items 1, 2, 3, 4, and M of Field L are the ones for which it might be most particularly useful to have a means of making distinctions of reference to Field J, H-1, or I.

5. Conflicts in Field H-2 (See Division 5 of Specific Directions and Explanations for Field G.)

For reasons explained in Field G, precedence is established for the three possible uses of Field H-2: (1) the site of a pathology in Field E, when the organ in Field H-1 is not the site of the pathology (accompanied by an asterisk coded in Column 30); (2) an organ, other than the site of the pathology, in a special state described by Symbols B, Ø, P, or S of Field L; (3) an organ other than the organ of Field H-1 to which the test compound is administered as indicated by coding in Field S-3.

6. An incidental pathological condition vs. a TREATED pathology

Symbols 5, 7, B, C, D, N, Ø, and S are used to code only pathological conditions which are not being treated with the test compound and which exist contemporarily with the pathology in Field E which is being treated with the test compound.

7. Adaptations (Symbol 1). (Refer to Division 7 of Specific Directions and Explanations of Field G, applying that explanation to Symbol 1 of Field L.)

8. Nutrient and hormone deficiencies and excesses, as incidental conditions vs. treated conditions

Field L is not used to code any pretreatment which brought about a pathological condition which was subsequently treated with the test compound for the test data being coded. In particular, any pretreatments producing deficiencies (extirpation of a gland, e. g.) which are to be treated experimentally with test compounds are not indicated in Field L; the deficiency pathology will be coded in Field E and if it were artificially induced for experimental purposes, the induction must be explained only in Field E--while Field L is left free for coding any experimental state incidental to this deficiency disease.

9. Coding of data from more than two tests using several host organism strains

Field J symbols (in contrast to Field E symbols) designate specific taxonomic strains. Therefore, there is no need for a symbol of Field L to indicate that a special taxonomic strain of host organism has been used in any one test. (See Division 12 below.) However, just as Symbol F in Field G is used to condense into two code lines data from several tests using several distinct strains of test organisms (ref. : Division 9 of Specific Directions and Explanations of Field G), Symbol F in Field L may be used to condense into two code lines data from several tests using several distinct strains of host organisms. The coder should refer to the part of Field G explaining this procedure, applying it to Fields J and L. To this extent (i. e. , to the extent that these several host strains may be taxonomic strains or varieties), Symbol F is used to distinguish in a non-specific way taxonomic strains, which represents an exception to the definition of the symbol implying that it is never used to indicate a taxonomic variety.

10. Pretreatments represented by Symbols 2, P, Q, and R; distinctions of definitions and use of the four symbols. (The explanation of these symbols is essentially the same as for Symbols 2, P, Q, and R of Field G. The coder is referred to Division 10 of Specific Directions and Explanations for Field G, applying that discussion to Symbols 2, P, Q, and R of Field L.)

11. Use of Symbols 6 and J; STATES OF resistance or sensitization to the test compound vs. PRODUCTION OF THOSE STATES

A. States of the host

(1) Sensitivity (Symbol 6)

Symbol 6 is used in Field L to indicate a sensitivity to the test compound having been produced in the host in Field J, in the same way as Symbol 6 of Field G is used when a similar sensitivity has been produced in the test organism. (Refer to Subdivision A of Division 11 of the Specific Directions and Explanations of Field G.)

(2) Resistance (Symbol J)

Symbol J is used in Field L to indicate that the host has been made resistant to whatever effects the test compound normally has on that host--EXCEPT the effect of relieving or curing the host of the pathology in Field E. In other words, if a test compound

demonstrates a given therapeutic action which diminishes after the initial therapy, this should not be described as a refractoriness of the host, but a refractoriness of the pathogen, non-infectious pathology, or tumor in Field E. The state of the pathology's having been made refractory to the test compound, when recording the test compound's action subsequent to the production of refractoriness, should be coded in Field G with Symbol J rather than in Field L. Any production of such refractoriness to the test compound should be recorded by a code line in which refractoriness production is coded in Field T-2, as described in the next paragraph.

B. Production of states of resistance and sensitivity of the host

Any actual production of resistant or sensitive states of a host organism would never be coded in a line in which that organism was coded as a host, but only by a code line in which the organism is coded in Field E as a test organism in which there was induced an increase in resistance or sensitivity to the test compound or a secondary compound (Field T-2 symbol, symbol series 51 or 58). The coding of increase of resistance and increase of sensitivity is described in Fields M and N, Division 11, in Fields W, X, and Y, Division 13, and in Field T-2, Division 20.

12. Symbols F, G, H, and I represent characteristics intrinsic to the host organism and do not represent responses to the test compound. (The coder is referred to Division 12 of Specific Directions and Explanations for Field G, which discussion can be applied to Symbols F, G, H, and I of Field L. These symbols are never used in Field L to distinguish taxonomic strains, although, in the case of Field J, there is no actual need, since Field J itself distinguishes taxonomic strains. See Division 9 above, however, for the special use of Symbol F in condensing data into two code lines.)

13. Host organisms, organs, or tissues with incidental IMPLANTS. (See Division 13 of the Specific Directions and Explanations for Field G. Example: Observations are reported on a compound's action on intestinal helminths in mice in which had been implanted tumors, the tumor implantation having been for the purpose of separate carcinostatic tests. In coding the anthelmintic action, the helminth would be coded in Field E, the mouse in Field J, the anthelmintic response and its evaluation in Fields T, X, and Y, and the fact that the host has an incidental implant [the tumor] is coded by Symbol S in Field L.)

14. Host IMPLANTED in a secondary host

Occasionally a test method involves maintaining the host (of the test organism) in a secondary host. While this is very unusual, though not impossible, in the case of whole organisms as hosts in chemical therapeutic tests, it is practically invariably the case that, when the "host" of the parasite, non-infectious pathology, or tumor is an excised organ or tissue of the host in Field J (indicated by Symbol R in Field L), that organ or tissue is maintained by a secondary, non-living "host" (i.e., a saline bath, nutrient medium, etc.).

Unfortunately, a second Field J is not provided for coding such a second host of the primary host organism. The few occasions when it would be needed do not justify it for the CBCC's coding. At most, a provision is made to express the fact that a secondary host is involved, without identifying it: Symbol T of Field L.

Since a non-living, secondary host is assumed for excised organ or tissue hosts, coding Field L with Symbol R carries that implication (expressed in the definition of Symbol R). The identity of the non-living secondary host (bath, nutrient medium, perfusate, etc.) should always be included in the written abstract of Field L.

Thus, Symbol T is available for use, however infrequent it may be, when the total host organism is maintained in a special secondary host organism or non-living secondary host. It is also used when this total host organism is a plant maintained in a special and basically unnatural medium for the experimental period (i.e., other than the soils in which it would be given optimum support, such as plant nutrient solutions, water, agar, perlite, sand, etc.)

15. Indications that an EXTIRPATED organ or tissue (site of pathology) is WHOLE (Symbol R) vs. the indication that the organ or tissue has been macerated, sliced, etc. (Symbols U, V, W, and X). (Refer to Division 15 of Specific Directions and Explanations for Field G, applying that discussion to Symbols R, U, V, W, and X of Field L.)

16. Symbols U, V, W, and X describe states of the host (or organ or tissue of the host) AT THE TIME OF CHEMICAL TREATMENT

When a compound is applied to a host organism (or organ or tissue site of pathology) which is later homogenized or made into slices or extracts, etc., for the purpose of reading the test results, Code Symbols U, V, W, and X can not be coded in Field L. This field is used only to describe the state or condition of the host or site of pathology at the time of treatment.

17. Symbol Y: resistance acquired to the test organism

This symbol represents a factor unique to Fields L and J in that the host can develop an immunity to the biological factor coded in Field E against which the test compound is being administered. This is a factor that frequently deserves or demands recognition in recording and evaluation of a therapeutic action of a test compound.

18. Symbol Z

This symbol is used in a unique way and does not correspond to the other symbols of Field L in that it does not represent just a pretreatment or state of the host during the test, but it represents, like the test compound, an active factor of therapy for the parasite, non-infectious pathology, or tumor. When this symbol is used, it indicates a therapeutic treatment given to the host (which may be in any experimental state indicated by any of Symbols 1 through Y), in conjunction with the test compound treatment (or test compound and secondary compound treatment). When any such test compounded of chemical and non-chemical treatment is coded, Symbol Z has precedence over any symbol for pretreatments and experimental states in Field L and the latter can only be recorded in the written abstract.

The CBCC Code makes no provision for identification of such non-chemical therapeutic treatment so that there is no way of distinguishing two or more tests (i. e., two or more code lines) according to variation in non-chemical therapy. A coding project concerned particularly with clinical data would doubtless find advantageous devising specific symbols, rather than a single non-specific symbol (Symbol Z), for various non-chemical therapeutic treatments.

19. Symbols available for additional items of Field L

All numerical and letter symbols available for Field L have been used. However, since the IBM zone punches have not been given special meanings in Field L, each of them can be used alone as a symbol.

20. File of coded biology data on IBM punched cards arranged according to symbols for experimental states of host

The CBCC has not established a special file of coded data in which Field L has been used (and arranged by Field L symbol sequence), because of the remote probabilities of a frequent need to search for all information on tests in which was a specific incidental condition of the host. The coding of Field L is more frequently used in "secondary" sorting of coded information and should be regarded as a means of recording biological aspects of chemical therapeutic tests that are frequently of prime significance in explaining the outcome, coded in Fields T, W, X, and Y.

21. Double coding is not possible in Field L

Having made use of all of numbers 1 through 9 and all 26 letters for code symbols in Field L, the IBM machine punching and retrieval procedures do not permit more than a single symbol in Field L in any one line. Therefore, when coding two or more tests whose details and outcomes are so nearly alike that the code lines for all tests would be identical except for differences in pretreatment or state of the host (Field L), the tests can not all be recorded by one code line with several entries (representing the several pretreatments or states) in Field L. (A special circumstance allows condensing

two or more tests in a single line by use of Symbol F of Field L [explained in Division 9], but this is not strictly comparable to double coding as it is described in the preceding sentence and even in this special case, Field L is occupied with but a single symbol.)

FIELD M
Columns 45 and 46

FIELD N
Columns 47 and 48

DOSAGE

FIELD M--PROPORTIONS OF TEST COMPOUND AND DILUENT:
I. E., CONCENTRATION OF TEST COMPOUND
ADMINISTERED TO THE TEST ORGANISM OR HOST

FIELD N--(1) QUANTITY OF PURE TEST COMPOUND ADMINISTERED;
(2) PROPORTIONS OF PURE TEST COMPOUND
PER UNIT OF TEST ORGANISM OR OF HOST

Organization

Fields M and N each have code symbols which consist of two units. These symbols are recorded by the CBCC in IBM punched card Columns 45 and 46 (Field M) and 47 and 48 (Field N). The first code unit in each field (Columns 45 and 47) designates the unit of measure in which the quantity is expressed (e. g., in Field M, parts per million, molar concentration, etc., and, in Field N, micrograms, milligrams, etc.). The second code unit of each field (Columns 46 and 48) indicates the actual quantitative value (e. g., in Field M, the number of parts per million, the number of millimoles per cubic centimeter, etc., and, in Field N, the number of micrograms or milligrams, etc.).

Thus, in both Fields M and N, a dosage is expressed by indicating (1) the unit of measure and (2) the measure or quantity itself. Providing code symbols for the first is merely a matter of assigning sequential numbers or letters to each unit of measure, such as Symbol 1 for parts per million, Symbol 2 for molar concentration, etc. The second, however, is not so simple as it may superficially appear. It is not practical to code specifically the numerical quantitative values themselves; therefore, code symbols must be assigned to represent ranges of quantitative values, such as a symbol which represents a range of 1 ppm to 5 ppm and another symbol for 5 ppm to 25 ppm, etc. Having made a definition for a symbol, such as > 1-5 ppm (i. e., any number of ppm more than 1 up to and including 5 ppm), it is thereby impossible to distinguish by code 2 ppm from 4 ppm; it is only possible, by code, to distinguish between ranges, so that a dosage can be indicated only as being in the range of > 1-5 ppm or > 5-25 ppm, etc. Defining these ranges resolves itself into a problem of determining reasonable limits of each range. This is intimately linked with the coding field used for recording evaluations of test results (Field Y). Since the difference between evaluations is sometimes solely a reflection of the amount of test compound administered, it is important that the ranges not be so broad that this difference in responses can not be explained in code by appropriate dosage symbols in Field M and/or N. Consider, as an illustration, a given test compound which caused a given response, but at a very low or insignificant degree at a dosage of 0. 1 units; not until 50 units was administered was the response optimal. Since the dosage value for this data will be coded as a range in which lies the smallest dose causing the highest response (50 units), it is important that the range in which 50 units lies is narrow enough so that doses causing less response or no response are not in the same range. If the range covered by a single code symbol were 1-100 units, for example, the fact that the most effective dose was 50 units, whereas 20 units, 5 units, 1 unit, etc., were less effective or totally ineffective, could not be distinguished by code. All such a code symbol would indicate would be that somewhere between 1 and 100 units, the test compound produced the response to the degree indicated in Field Y. However, if the definition of a code symbol were a range of only 30-60, the use of that symbol would indicate at least that somewhere between 30 and 60 was the dose producing the response of the degree indicated in Field Y and that below 30 the response occurred at a lower degree or not at all. Thus, the more narrow the range represented by each code symbol, the more precise can be the coding of dosage administered producing the response to the degree coded in Field Y.

Because of the relationship between the dosage fields (Fields M and N) and the evaluation field (Field Y) and because in Field Y the symbols available for evaluation coding are only digits 0 and 1-9, the only symbols correspondingly permitted in Columns 46 and 48 of Field M and N are 0 and 1-9. The value scales are divided, therefore, into 9 (or rarely 10) consecutive ranges. (Reference should be

made to the discussion of Fields X and Y for a more complete account of coding evaluations and their interpretations.)

If a compound causes a given biological response (coded in Fields T and Y) when administered in very small quantities, it is indicative of a more highly sensitive biological system or a more highly active or efficient test compound than if that same response were achieved only by administering more massive doses. Further, when concerned with such sensitive responses, it is usually the case that the dose producing a given response is a more critical factor demanding a nicer distinction than when the biological response is only with large doses. For these reasons, the division of the total range of quantitative values has been basically by logarithmic progressions which provides wide ranges at the upper end of the scale and narrow ranges at the lower end (e. g. , >625 through 2, 525 ppm [Symbol 8] and 0. 04 through 0. 2 ppm [Symbol 2]).

The total range for any given unit of measure (i. e. , for any given scale of quantities) is not necessarily consistent with total ranges for other units of measure. For example, in Field M, the scale for parts per million (Scale 1) ranges from <. 04 to >2, 525 ppm (= . 000004% to >. 2525%), whereas the scale for per cent weight or volume (Scale 4) ranges from >. 000001% to 100% (= . 01 ppm to 1, 000, 000 ppm) so that the percentage range (Scale 4) is broader than the parts per million range (Scale 1) and the individual symbols for the quantitative values, therefore, describe broader ranges of percentage values (Scale 4) than they do ranges of ppm (Scale 1). The reason for the difference in the case of these two total ranges is simply that an author's use of the unit, ppm, is ordinarily confined to expressing measurements of administered doses when they are of a fine and critical nature. When greater concentrations are used (e. g. , 10, 000, 100, 000, or 1, 000, 000 ppm), an author seldom expresses it in ppm, but in percentage concentration. Therefore, it was reasonable to set the limits of the total range for ppm closer than the limits of the total range for percentage and the advantage thereby gained for the ppm scale was a finer division into ranges for the quantitative symbols of the scale. The significant point to be observed is that in two or more scales which are comparable in that the quantitative values of one can be converted to quantitative values of the other (e. g. , 100 ppm can be converted to 0. 01%), the quantitative code symbols do not represent the identical quantitative ranges and are not therefore interchangeable so that whereas 100 ppm is coded with Symbol 6 by the ppm scale (Scale 1), it would be coded with Symbol 5 by the percentage scale (Scale 4). In Field N, Scales 1 and 2 do not have identical or even similar range limits. In this case, the two scales represent a continuum and do not overlap at all, essentially for the same reasons as for the difference in ranges of Scales 1 and 4 of Field M. In the case of Scales 1, 2, and 4 of Field N, by spreading the total range across the three, each scale benefits by having a more narrow range for each quantitative symbol than if each scale attempted covering the total range.

It should be recorded that the scales for those units of measure expressing quantity of pure test compound per unit of test organism or per unit of host organism or host environment (e. g. , mg/kg, mg/sq. ft. , lbs/acre) might have been placed in Field M, since the pure test compound in such cases is understood to be distributed over or through the organism or environment on or into which it is placed and therefore the expressions are indicative of a final concentration of the test compound of which the organism or host environment serves as the diluent. If this were done, the definitions of and distinctions between the uses of the two Fields, M and N, would be altered. The fields would permit distinguishing between (I) any expression of "concentration" (either "initial" or "final") (in Field M) and (II) any expression of "quantity of pure compound disregarding organism or host environment size" (in Field N). This distinction seems of less advantage or significance than the distinction according to whether there can be indicated (1) the administration of the compound at a given concentration, although the final total amount is not implied, as opposed to (2) the specific final total amount of compound applied (whether expressed as a total quantity per test organism, host, or host environment or as a total quantity per unit of test organism, host, or host environment). Therefore, this latter distinction has been the basis for definitions of Fields M and N, respectively, and accordingly the scales for quantity per unit of test organism, host, or host environment are in Field N. Thus, with these definitions, when only Field M is coded, it may be assumed that nothing is known except the concentration of the test compound in the preparation administered; the total amount administered is not known. However, when Field N is coded, either alone or with Field M, there is indicated that actual quantity of test compound administered to the test organism, host, or host environment, according to which of these three the administration was directly made.

General Use

Field M is used in cases when the test compound is applied in a diluent or carrier so that the quantity must be expressed in terms of a concentration of the test compound in the preparation administered. In case a compound is administered at 100% concentration (i.e., lacking any diluent) and the quantity is unknown so that it can not be expressed in Field N, Field M may be coded with Scale 4, Symbol 9.

Field N expresses the amount of pure compound administered to the biological component of the test within a given unit of time expressed in Fields O and P. This field is used, therefore, when the test compound is applied in a pure and undiluted form--so that the concentration is always 100%--and when the quantity of this is known. However, Field N is also used to express the amount of pure compound represented by the total dose when administered at a given concentration less than 100% (the concentration being always expressed in Field M). The quantity in any case is always expressed in Field N in terms of amounts of the pure compound, such as pounds, grams, milligrams, etc.

Specific Directions and Explanations

1. Both concentration and quantity coded when possible

An author will seldom record both the concentration of the test compound preparation employed and the quantity of the test compound applied per organism, but he will often give information on the concentration in such a way that the quantity applied per organism can be calculated or will give quantity-dosage information from which concentration-dosage information can be calculated. When both concentration-dosage and quantity-dosage information are available or can be calculated, both should be recorded and coded.

2. Selection of the scale (i.e., the unit of measure) when the author's unit of measure can be converted; Field M Scales 1, 4, B, and 5

In Field M, some concentrations can be expressed, though not equally well in all cases, with any one of several scales by mathematically converting the dosage values. These are Scales 1, 4, and B. (Scale 5 represents a unit of measure, pounds/100 gallons, which can be converted to the units of measure of Scales 1, 4, and B, but the probabilities of frequency of such conversion is very remote.) In Field N, none of the scales represent units of measure that can be converted to the unit of measure of another scale, except that when a dose of more than 81 micrograms (= 0.081 milligrams) is administered, for example, Scale 2 (the milligram scale) or Scale 4 (the gram scale) is used, since the microgram scale range is limited to a maximum of 81 micrograms and the milligram scale begins with 0.081 milligrams (= 81 micrograms). Therefore, a dose of 200 micrograms, for example, would be "converted" to 0.2 milligrams and coded by Scale 2. In the case of Field M, when an author expresses dosage in units other than those represented by Scales 1, 4, 5, and B, there is no choice but to use the scale for the unit of measure used by the author.

In regard to making a choice of one of the Scales, 1, 4, B, and 5, of Field M, there should be considered whether greater accuracy of expression can be made with one of the scales. As an illustration, 4000 ppm (Scale 1 of Field M) would seldom be coded by use of Scale 1, since it could only be interpreted as > 2525 and it might therefore represent any concentration from 2526 to 1,000,000 ppm. By converting it to 0.4%, it can be coded so that its interpretation is at least limited to between 0.1% and 1.0% (Scale 4). Within the overlapping parts of the total ranges of Scales 1, 4, and B, it is probably not too important as to which scale is used. For example, 100 ppm might be converted to 0.01% or to 0.1 mg/ml and, in code, this would be Symbols 16, 45, or B5, respectively. Thus, the code symbol for the quantity unit (underlined in the symbols) varies only by one digit (or at most two, with other dosage values) and this difference is not actually significant to evaluation when it is based on dosage (Field Y), since such evaluation accuracy is not pretended by this Code.

Occasionally, when data are being coded from a research program in which many compounds were tested by a single method, it is desirable to code them so that the coding is comparable for all tests of that particular testing program. A single scale most suitable to the data has been selected by the CBCC in such cases and used consistently (e.g., Scale 1, ppm) even if some of the tests used dosages which are beyond the maximum limit of the scale's range (e.g., beyond 2525 ppm).

When two or more of the four scales of Field M (Scales 1, 4, 5, and B) seem equally adequate for expressing the dosage quantitatively, the field of biology which the data concern should be considered. Thus, if one of the units of measure seems a more reasonable expression of the dosage, because that measure is more commonly used in that biological field, the choice should be made on that basis. For example, pounds per 100 gallons (Scale 5) is the unit of measure most conspicuously inappropriate for pharmacological data.

In Field N, it is always best to express the dosage given per unit area or per unit mass of the test organism (or host, if administration is to a host) when this is possible. A practical example is the intravascular injection of 2 mg per 20-mg mouse (when each test mouse has been selected for approximately 20 grams weight). In this case, it is possible to code merely that the dose was 2 mg, with Scale 2 of Field N; however, in this expression, there is no correlation of the mass of the organism with the given dose. The difference between distribution of 2 mg through 20 grams of mouse and 40 grams of mouse (or through the 20-pound mass of a larger animal) is considerable and thus a scale which represents a correlation between the dose and the organism size permits a more accurate statement of the dosage to which each unit of the organism was exposed. Therefore, the CBCC coder would calculate the per-kilogram dosage and use Scale 6.

3. Dosage size as a basis for evaluation of a specific action or use

Evaluation (Field Y) of a given chemical activity (Field T) based solely on dosage (Fields M and N) is actually not possible unless test data on only one type of biological activity were being collected and the experimental method remained comparatively standard. This is because compounds tested for certain practical uses (agricultural chemicals, e.g.) may deserve a high activity evaluation when applied in comparatively large doses (because under the conditions of practical application only such large applications of known chemicals produce the response). If the test evaluation of compounds for such a practical use were made by reference to a standard dosage scale which was designed to permit expression of test doses for all possible test data, the evaluation would be misleading, for it would indicate only that since the dose was high, the relative chemical activity was poor and although this may be chemically-biologically true, it is not an adequate expression of the evaluation of the compound for the use for which it was tested. Although the preceding will be discussed again in Field Y, it is pointed out here to permit explaining more clearly that the use of symbols assigned to the nine ranges of each scale is primarily for expressing the most effective (or highest ineffective) dose administered. The symbols can not be used as a sole means of arriving at the evaluation of the compound for the specific action (i.e., the specific use) for which it was tested. It might only be used this way if data on a single specific action were being collected, coded, and filed and if the dosage scale had been adjusted to evaluate chemicals for this one activity on a comparative basis. (See also the discussion of the organization of Field P.)

Relative to the above statements, however, the final observation should be made that use of such a scale as a basis in evaluating responses from test data on any and all chemical actions, would not be entirely without significance, since there would be expressed thereby the comparative basic sensitivities of the biological systems involved to each compound tested, varying only by the application method.

4. Dosage to be coded when application is to the (1) test organism, (2) host, or (3) parent

When application of the test compound is made directly to the test organism, even if it is in or on a host, the dosage to be coded in Fields M and N is that dosage applied to the test organism. If the test organism is in or on a host or host environment coded in Field J and the application of the test compound is directly to the host or host environment (and therefore only indirectly to the test organism), the dosage coded in Fields M and N is the dosage applied to the host. Provision is made Through Field S for application to an egg or developing embryo when the application is only indirectly to the egg or embryonic stage but directly to the parent while the young stage is still intimately

connected to the parent: The dosage applied to the parent is recorded in Fields M and N and the fact that the response is read on the embryo or offspring (coded in Fields E and F) is indicated by Symbol Ø in Field S-3.

5. Relationship between the dosage fields (Fields M and N) and Fields H and I; use of Symbol # when Field J is NOT coded. (See Divisions 6, 8, and 9 for the use of zone punches when Field J IS coded.)

Occasionally, data are encountered in which the test compound was applied to a test organism to determine the effect on some component organ or cell of the test organism and the author has determined the actual concentration of the test compound, at the site of action within the organism, to which that organ or cell is exposed. For example, a 1% solution is administered to a test organism in a volume calculated to give a final dose of 10 mg/kg. An analysis revealed a blood level of 0.1 mg/cc. The action was on leucocytes. In this case, since the action is stipulated as being local and at the organ where the 0.1 mg/cc concentration existed, the dosage to be coded is the 0.1 mg/cc. The dosage administered to the gross organism (1% solution to give 10 mg/kg) is not coded, though it should be included in the written abstract as a record of the technique that gave the 0.1 mg/cc blood level.

In such cases, the administration must no longer be regarded as being to the test organism (Field E) whose component was affected. Instead, it is the concentration to which the test organism component, the organ (Field H) or tissue (Field I), is exposed. For this reason, the IBM 11 zone punch (Code Symbol #) is used in the dosage fields, Columns 46 and/or 48, to give this special meaning to the dosage entry. Thus, when Field J is not coded and the Fields M and/or N are coded with Symbol #, the dosage coded is interpreted as the dose applied to the organ or tissue in Fields H or I and is not the dose applied to the gross test organism in Field E. (See the diagram of Division 9.)

6. Significance of the relationship between the coding in the dosage fields (Fields M and N) and Field J; use of Symbol # (IBM 11 zone punch) when Field J is coded

In nearly all cases when Field J is coded, administration of the test compound to that host or host environment is implied and it is assumed that the organism, pathology, or tumor in Field E received the test compound only to the same degree as any neighboring part of its host or host environment. In those more rare instances, when Field J is coded with a host or host environment, yet (1) application is actually directly to a test organism or tumor or pathological organ so that influence of the dosage expressed is fully upon the test organism, tumor, or diseased organ or (2) the author has determined the final concentration of the test compound in the host or host environment (although application is directly to the host or host environment) so that the dosage expressed is the actual concentration to which the organism, pathology, or tumor in Field E is exposed, a coding expedient has been resorted to for indicating it. The IBM 11 zone punch, coded by the symbol #, is used in Fields M and N, Columns 46 and 48, to indicate that the coded dose was not the dose administered to the host coded in Field J but was the dose to which the organism, tumor, or disease coded in Field E was directly exposed, regardless of the actual route of administration indicated in Field S-3.

Symbol # is used in Fields M and N when a host is coded in Field J and--

(1) the application is to the test organism and the dosage is expressed as a concentration or quantity to which the test organism is exposed, although the test organism is attached to a host coded in Field J, or--

(2) the application is to the host but the dosage expressed is the concentration to which the test organism (Field E) is exposed.

Symbol # is not used in Fields M and N when a host is coded in Field J and the application is to the host in terms of quantity per unit of the host (e.g., mg/kg, gal/acre, etc.). Although this is admittedly an expression of the concentration to which the test organism is exposed (as in situation 2 above), the terms of the quantity-per-unit-of-organism-or-environment scales are applicable to the host. (I.e., when administration is to the host or host environment, the terms of the scales represent quantity per unit of host or host environment, not quantity per unit of test organism.) Symbol # would only be used with these scales (under circumstances of Field J being coded) if the application were to the test organism and the dosage was therefore in terms of quantity per unit of the test organism (as in situation 1 above). See Division 5 above and Division 9 for the use of Symbol # when Field J is not coded.

7. Dosage to be coded when the test compound is added to and distributed through a host MEDIUM and the final concentration is determined

When a test compound is added to a host environment (i. e., the environment of a test organism) coded in Field J (e. g., a nutrient medium, a natural environment such as water or air, the fluid of a tissue or cell suspension, etc.), the dosage to be coded in Fields M and N is preferably the concentration after complete dispersion in this host, whenever this is known or can be calculated. (This is also discussed in Division 6 above as Situation [2].) When this final concentration is coded in Fields M and N as the dosage, the administration of that recorded concentration can no longer be regarded as being to the host environment coded in Field J but must be regarded as being to the test organism in Field E. Therefore, it is appropriate that all coding in Fields A, B, and C must describe the state after distribution through the test organism's environmental medium; the state and any solvents of the test compound prior to introduction to the host environment will not be coded. By coding the Symbol # in Fields M and/or N (whichever is used), the fact is indicated that the host coded in Field J is actually the diluent and that the coded dose is the dose applied to the test organism or tumor coded in Field E.

If a test compound is applied to such a host environment or culture medium and only the quantity or concentration initially given to the medium is known (i. e., the final concentration in the medium is unknown), the dose coded in Fields M and N will be that given to the medium, Fields M and N will not be coded with Symbol # and coding in Fields A, B, and C will describe the state when added to the medium. For example, if the concentration is given in terms of a gas which is subsequently streamed through, or otherwise exposed to, (1) a bath or perfusate of a tissue macerate or (2) an enzyme-containing secretion (e. g., milk), the concentration of the applied gas may be coded in Field M, regardless of the unknown factor of its solubility. In this case, Field A must be coded with "gas", Symbol 1, and Fields B and C would not be coded, since the test compound was not in a solvent or conditioning agent when it was added to the host liquid. If, however, the author should actually have determined the dissolved concentration of the test compound, coding in Fields M and N should be based on that concentration with the Symbol # in Columns 46 and/or 48, Field A coded with "solution", and Field C is coded with the bath (water, saline, etc.).

8. Relationship between the dosage fields (Fields M and N) and Fields E, H, and I when Field J is coded; use of Symbol 0 (IBM 0 zone punch) when Field J is coded

A further provision is stipulated for a testing situation that is doubtless infrequent. It is described with the belief that by presenting and discussing all possible situations and all relations with other fields, the pattern of coding Fields M and N will be better comprehended. If an author has determined by some analytical procedure the actual amount of test compound at the site of action when the action is on an organ, tissue or cell structure of the test organism in Field E and this test organism is maintained in a host coded in Field J (living or non-living), that dosage should be the one coded in Fields M and N, rather than the amount given to the gross host or the gross test organism. In this case, the IBM zone punch 0 is coded in Fields M and/or N, Columns 46 and/or 48, to designate that it is not the dose applied to the host in Field J nor the dose applied to the gross test organism in Field E, but it is the dose present at the organ or tissue site of action in the test organism. This organ or tissue may or may not be the organ or tissue coded in Fields H and I, as explained in the following two paragraphs.

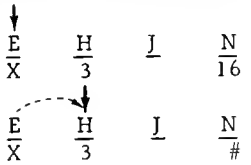
It will be recalled that if a culture medium or environment (i. e., a non-living host) is coded in Field J, it is so indicated by the IBM 0 zone punch in Column 37 of Field J (i. e., by the use of code symbols beginning with any of letters S through Z in Field J) and this is in turn an indication that any accompanying coding in Fields H and I represents organs or tissues or cell parts of the test organism in Field E rather than of the entry in Field J. Therefore, when Fields M and N are coded with the zone punch 0 in Columns 46 or 48, and Field J is coded with symbols beginning with any of letters S-Z in Column 37 (i. e., is also coded with zone punch 0), the organ, tissue, or cell part to which the coded dose is applied will be the structure coded in Fields H and I.

However, when Fields M and N are coded with the zone punch 0 in Columns 46 and 48, and Field J is coded with symbols beginning with anything other than S-Z, the organ, tissue, or cell part

to which the coded dose is applied is only suggested by the coding in Field T-2, since in this case the coding in Fields H and I indicate only the location of the test organism, tumor, or pathology in the host.

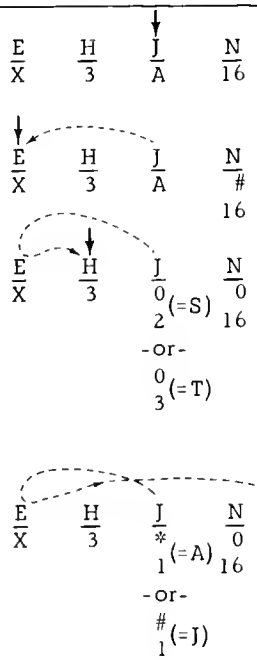
9. Summary of Relations between Fields M and N and Fields J, E, M, and I and the use of Symbols # and 0 in Columns 46 and 48 as described in Divisions 6, 7, 8, and 9

The following is a diagrammatic explanation of the coding procedure (or interpretation of coding) indicating the organism or structure to which the dose, as coded in Fields M and N, applies. The vertical arrow indicates in each case the field to which the dose coded in Field M or N applies. (Only Field N is used in these diagrams.) The curved, broken-line arrows indicate the shift in meaning which is given by the zone punches in Fields M and N.



With no zone punch in Field N (or M), the site of the dosage is directly to or in the test organism in Field E.

With the 11 zone punch in Field N (or M), the site of the dosage is directly to or at the anatomical part coded in Field H (or I) instead of the organism in toto in Field E. (See Division 5.)



With no zone punch in Field N (or M), the site of the dosage is directly to or in the host (living or non-living), in Field J.

With the 11 zone punch in Field N (or M), the site of the dosage is directly to or in the test organism in Field E instead of the host in Field J. (See Divisions 6 and 7.)

With the 0 zone punch in Field N (or M) and Field J coded with a symbol beginning with any of letters S-Z (Symbol S, e.g., is formed by IBM 2 punch plus the 0 zone punch in Field J; Symbol T by the 3 punch plus the 0 zone punch, etc.), the site of the dosage is directly to or at the test organism's anatomical part coded in Field H (or I) instead of either the host in Field J or the test organism in Field E. (See Division 8, first two paragraphs.)

With the 0 zone punch in Field N (or M) and Field J coded with a symbol beginning with any of letters 1-9 or A-R, the site of the dosage is directly to or in none of the host in Field J, the test organism in Field E, or the anatomy coded in Field H (or I), but the coding in Field T-2 may suggest the site. (See Division 8, last paragraph.)

10. Dosage given in terms of the biologically active portion of the test compound molecule; use of Symbol * (the IBM 12 zone punch) in Column 46 or 48

Occasionally, an author expresses a dosage in terms of the part of the molecule that is known to be the biologically active portion. For example, in calculating the dosage of a test compound which is administered as any one of several salts, the dosage is calculated on the molecular weight of the base of the compound regardless of the total weight of the entire salt molecule. Since the total compound used must be regarded as the test compound, such as a salt, the fact that the dosage is not expressed as a weight-or volume of that total test compound, but only as the biologically active portion, is distinctively indicated by using the 12-zone punch, coded by Symbol *, in Columns 46 or 48 or both.

11. Dosage (amount administered per unit time) to be coded when, during a test, the dose per unit time is altered; discussion of coding production of "tolerance" and "sensitivity" (induction of tolerance increase and sensitization)

If the dosage is deliberately varied so that two or more are used in sequence in a single test run (i.e., so that essentially two regimens are employed), frequently more significance can be attached to one dose than to the other and that may be coded in preference to leaving Fields M and N uncoded. Consider the following example: 1.0 ml given daily for two days followed by 0.05 ml given daily until evaluation was made two weeks after beginning of treatment. In this example, the dose given over the longest period of time might be coded, though, if a large number of compounds were being tested and the comparison was on the basis of the most efficacious initial dose or if the initial dose level of a single compound were varied with consecutive test runs to find its most efficacious level, the initial dose would be the most sensibly coded. In any case, under these circumstances of such a varied dosage regimen, no evaluation of the line should be based on the entry of Field M or N.

Because the phenomenon of an organism's developing an increased tolerance to a test compound (Field T-2, Symbol 51) involves administration of two or more doses, frequently at two or more levels, it will be discussed thoroughly here rather than in Field T-2. In this discussion, tolerated doses refer to sub-threshold doses for any detrimental response and not just to sub-lethal doses. Unless the reader is specifically interested in the coding of tolerance or sensitivity, it is suggested that the remaining rather involved explanations of this division be disregarded.

A. Tolerance increase:

An increased tolerance may be evidenced by only the test observation that the same dose level given repeatedly over a period of time elicits increasingly lower response. In this case, when the test dose remains constant and the response diminishes, code Fields M and N with the single dose level, Fields O and P with the administration schedule, and Fields T-1 and T-2 with "causes increased tolerance" (T-1 1, T-2 51). The evaluation is ordinarily with Criterion 01 in Field X with Symbol 0 in Field Y, except that if the actual per cent decrease in response is reported or can be calculated, Criterion 62 may be used. If the time to produce threshold decrease in response is the basis for evaluation, one of the criteria basing evaluation on time values may be used.

On the other hand, a test compound might be administered for the express purpose of determining the ability of the test organism to develop an increased tolerance of any degree or for determining to what actual maximum level the tolerance may be increased. This is done by the technique of giving a series of doses which may be uniform in size but are usually of increasing size and which may be maximum tolerated doses or may be doses below the maximum tolerated level. Regardless of size of the dosage series administered to bring about increased tolerance, the final determination of the increase in tolerance is by administration of a dose larger than the original maximum tolerated dose to determine if the latter has been significantly raised. When an increase in tolerance (increase in resistance) is thereby in evidence, the CBCC codes, as a convention, the highest level shown to be tolerated (either a new tolerated level or new maximum tolerated level), but when there is indicated no increase in tolerance (no increase in resistance), Fields M and N are coded with the lowest dose not tolerated. The lower dosages used to develop this tolerance increase are not coded in Fields M and N, but are included in the written abstract. With this test method in which essentially the test dose is increased in pursuance of a diminishing response (when the increase in tolerance is expressed as the increase in dosage tolerated rather than the decrease in response to a given dosage), the criteria of Field X that may be used to evaluate tolerance production to the level of tolerance indicated by the dose in Fields M and N are limited and, in particular, Criteria 20 and 21 are not to be used. Criterion 20 (Minimum Effective Dose) is inappropriate, because the dose being coded is instead the tolerated dose or the maximum tolerated dose after any tolerance increase. Criterion 21 (Maximum Tolerated Dose) is inappropriate, because the CBCC prefers to define all maximum tolerated doses as applying to normal test organisms (organisms with no acquired tolerance). Also, the evaluation of tolerance increase should be based on the degree of elevation of tolerance to the test compound. Evaluation of tolerance increase is by comparing the original maximum tolerated level (not coded) to the final tolerated level (coded), when these are known, using Criterion 18; if only one of these levels is given, Criterion 01 is used, indicating either no tolerance increase by Symbol 1 of Field Y (in which case the dose coded in Fields M and N is the lowest final dose to which the test organism was not tolerant) or positive tolerance production by Symbol 0 of Field Y (in which case the dose coded in Fields M

and N is the highest final dose to which the test organism was shown to be tolerant). In addition, tolerance increase might conceivably be evaluated by Criteria 10, 11, 12, 13, etc., when appropriate time values are determined and are the author's basis for the test evaluation: duration of administration needed to bring the organism's tolerance to the level indicated in Fields M and N or duration of the increased tolerance level.

If, however, the author were to have demonstrated a minimal dose which would initiate or induce tolerance of the organism to the test compound, Field X is always coded with Criterion 20 (Threshold Dose), and Fields M and N are coded with that minimal dose.

B. Sensitivity increase:

The development of sensitivity of an organism to a test compound is understood to be essentially the reverse of development of tolerance in that the organism becomes less tolerant to (i. e., becomes more sensitive to) the test compound by an initial exposure or exposures to the test compound. This increased sensitivity is induced by an initial administration of the test compound. It is revealed by a second or more doses in which a biological response appears which either did not occur with the initial dose or which appeared to a greater degree than with the initial dose. As in the case of coding increase-of-tolerance data, coding increase-of-sensitivity data depends on the test technique and the way the evidence for a sensitivity increase or for production of a sensitive reaction is expressed.

If the author merely states that the organism has developed an increased sensitivity or a specific sensitive response to the test compound during a program of administration, code in Fields M and N the lowest dose demonstrated to cause the sensitive reaction, code "causes increased sensitivity" in the action fields (T-1 2, T-2 51), and Criterion 01 in Field X. If there is determined a measure of sensitivity production or sensitivity increase (i. e., a new, lower maximum tolerated dose after sensitization), it may be expressed as (1) an increase in response with each successive administration of the same dose (assuming that doses are spaced so that the response is evidence of increased sensitivity) or (2) the appearance of a response after a second or more administrations of the same dose. In this instance, Fields M and N are coded with the dose demonstrated to elicit the sensitivity; Field X is coded with Criterion 01, if the exposure results in the initial appearance of a sensitivity response or if the per cent increase in sensitivity response is unknown, or with Criterion 61 or 62, if the per cent increase in sensitivity response is known. The sensitivity production or increase might also conceivably be expressed as a decrease in dosage necessary to maintain a response of a given degree or decrease in dosage necessary to prevent a given response (i. e., a decrease in the threshold and maximum tolerated doses). In this case, Fields M and N are coded with the lowest level to which this threshold dose or maximum tolerated dose has declined and Field X is coded with Criterion 01, or, if the original and final dose levels are known, Criterion 19 may be used.

If the author should have demonstrated a minimum dose which will induce an increase of sensitivity, that dose may be coded in Fields M and N with Criterion 20 in Field Y. Only in this case should Criterion 20 be used with sensitivity data.

Sensitization: The term "sensitization" is most often used in reference to a specific immunological phenomenon as defined in the Code by Symbol 58. When the test organism is sensitized to the test compound and Symbol 58 is used in Field T-2, Fields M and N are coded with the sensitizing dose. The typical responses (allergy, anaphylactic shock, etc.) to the test compound on subsequent exposure are coded as such in Field T-2 and the dose coded in Fields M and N is the dose needed to elicit these responses after sensitization.

12. Dosage to be coded when the test compound is part of a formulation or when a mixture of test compounds is administered

The CBCC has avoided treating formulations as specific test compounds, for a number of reasons. Therefore, when biology data are coded from tests using formulations, the single active component of the formulation must be known. That single component is coded as the test compound, Field B is coded with Symbol 6 (signifying that the compound is administered as part of a formulation, but that the dose coded in Fields M and N and the evaluation are based on the test compound itself), and Fields M and N are coded with the calculated amount of the test compound, not the amount of the

total formulation. If the amount of the test compound (the active ingredient of the formulation) can not be determined, Fields M and N should not be coded.

If it should be desirable to code data from tests using formulations in which the active ingredients are not specified, so that the "test compound" is only a proprietary formulation name, the procedure would have to be different: The formulation name would be coded as the "test compound", Field B would not be coded with Symbol 6 (since, in this case, the test compound is the formulation and is not a part of a formulation), and Fields M and N would be coded with the dosage based on the total formulation.

The CBCC has coded data from tests using mixtures (i. e., two or more test compounds known to be active and administered together or two or more test compounds, all candidate for the activity and administered together), but with considerable reserve. When it has seemed appropriate to include such test data, Field B is coded with Symbol 0 (to indicate that the compound coded as being the test compound is actually only one of two or more compounds of a mixture and that the dosage in Fields M and N and the evaluation are based on the total mixture) and Fields M and N are coded with the amount of the total mixture administered. Subsequently, additional code sheets (and IBM cards) are made for each of the other compounds, recording the same biology test data.

13. Relation between Field N and Fields O and P

Frequent coding errors justify taking the precaution of examining carefully the coding in Fields N, O, and P. The quantity coded in Field N should never be more than the quantity administered within the time interval coded in Field O. The total dose given over the period of the test is the product of the dose in Field N multiplied by the frequency in Field O multiplied by the duration in Field P.

14. Coding of ad libitum feeding in Fields M, N, O, P, and S

In coding information on ad libitum feeding, record and code in Field M the concentration of the test compound in the food. The fact that the test compound is consumed ad libitum is indicated in Field O by Symbol 2 and in Field S-3 by Symbol 4; the duration of the consumption of the test compound (i. e., the time from presentation of the food-test compound mixture and its withdrawal from the animal) is coded in Field P. However, if after a period of ad libitum administration, the daily or weekly intake of the test compound is determined or can be calculated, that daily or weekly intake is coded in Fields M and N, the appropriate time interval (one day or one week, etc.) is coded in Field O, the total duration is coded in Field P, and Field S-3 is coded with Symbol 2.

15. Relations between Fields M and N and Field Y; double coding in Fields M and N

The ultimate concern of the discussion of this Division is with the collective data from two or more consecutive tests in each of which a different dosage level of the test compound has been administered in an effort to discover an active level (or a tolerated level) or the most effective level (or the highest tolerated level). (Division 11 discusses coding of data from tests in which more than one level of the test compound were administered as a series in the same test.) Before describing the procedure for coding the collective data from such a series of tests, the characteristics of the two fields, the dosage field (i. e., Fields M and N) and the evaluation field (Field Y), and the relationships between them will be briefly reviewed.

As mentioned in the section discussing organization of Fields M and N, quantitative values are reduced to code by dividing them into ranges, each range being assigned a code symbol. This is not exclusively true for Fields M and N. Other fields dealing with quantitative values must be similarly organized into code symbols, notably Fields P, Q, U, V, and Y. Any single code symbol representing a quantitative value is therefore only as precise as the narrowness of the range it represents allows. I. e., a symbol in Field N representing 50 to 60 mgs would code 55 mgs more precisely than would a symbol representing 1-100 mgs. In Field Y, a symbol representing evaluation of a 2-3 hours killing time would code more precisely the evaluation of a 2-hour killing time than a symbol representing evaluation of a 1-5 hours killing time. It will be helpful if in the following discussion this fact is kept in mind--that each symbol in Fields M, N, and Y represents not a single value, but a range of quantitative values.

FIELDS M and N
Columns 45 and 46;
47 and 48

The relation between Fields M and N and Field Y will be understood by considering a single symbol in Field Y, e.g., Symbol 3, which represents a specified range of effectiveness, e.g., 31-40% mortality. It frequently happens that two or more dosage levels (Fields M and N) may cause responses lying within this one evaluation range (Field Y); for example, one dose may cause 32% mortality while a higher dose may cause 39% mortality. Since either of these response evaluations would be coded in Field Y with Symbol 3, they can not be distinguished by code. I.e., the distinction between 32% and 39% is beyond the discrimination given significance by the CBCC Code, by virtue of the Code's having established the particular limits of this coding range as 31% and 40%. In this example, all test doses producing 31-40% kill are to be coded. To state this more broadly, all doses should be coded which have been shown to produce any response that falls within the definition of the symbol coded in Field Y as the evaluation.

It must be remembered that dosages in Fields M and N are also expressed by symbols representing ranges and reference should be made to the discussion of this under the section describing the organization of these dosage fields. If all doses which produce various responses lying within a single evaluation range in Field Y lie within a single dosage range in Field M or N, all of the data are represented by a single code line and distinctions between the dosage levels and the corresponding response evaluation are indicated only in the written abstract. If, however, the two or more doses producing the responses which are coded by the same symbol in Field Y do not lie within a single dosage range in Field M or N, each of the dosage ranges must be coded. This might be accomplished by either of two procedures (although of the two, the CBCC has always used the more practical, abbreviated procedure). To construct a separate code line for each of the dose ranges in which are dose levels giving results coded by a single Field Y symbol, each line differing only by the entry in Fields M and N, would be extravagant of time. As an alternative to this, the CBCC procedure is to code in Fields M and N, in a single code line, all the information that would otherwise be given by coding two or more separate lines. This is done by determining which doses, of all those tested, produced the single optimum response evaluation coded in Field Y. If there are two such dose ranges involved (e.g., 24 and 25 in Field N, representing 5 mg and 10 mg), both are coded in Fields M and N, by coding one above the other in the same coding box in the same line. The CBCC refers to this as double coding and both entries are punched on the same IBM card. If doses which produced the response coded by a single symbol in Field Y are in more than two dosage ranges (e.g., 24, 25, 26, in Field N, representing 5, 10, 25, and 50 mg doses in 4 tests), the highest and lowest ranges (e.g., 24 and 26) should be coded in Fields M and/or N.

16. Special considerations for the procedure of double coding in Fields M and N; relation of Field X to Fields M, N, and Y

Relative to the situation requiring double coding in Fields M and N, described in Division 15 above, is the special situation when the criterion for evaluation is based on a percentage response (Criteria 51 through 59 and Criterion 62, coded in Field X) and 100% response results from administered doses. When several doses have been demonstrated to produce high responses, all of which are coded by a single symbol in Field Y, and one or more of these doses produce 100% response and the doses producing the several responses coded by a single symbol in Field Y fall within two or more ranges in Fields M and N, the CBCC considers, for coding, only those doses which produce less than 100% response. For example, 5, 10, 25, 50, 100, 150, and 250 mg doses produced respectively 55%, 85%, 95%, 95%, 100%, 100%, and 100% responses. Since it is reasonable that optimum doses be described as the lowest producing the highest response, the doses to be considered here seem to be 25, 50, and 100 mgs, since 100 mgs is the lowest dose producing 100% response and responses of 95% and 100% (produced by 25, 50, and 100 mg) are all coded by the same symbol in Field Y. However, for specific reasons, the CBCC considers only doses giving less than 100%, as stated above; therefore, in this case, only 25 and 50 mg producing 95% response would be considered. Field N would be double coded with Symbols 25 and 26 (the two dose ranges in which are included the two doses) and Field Y would be coded with a single symbol, either Symbol 9 (when using Criterion 62 in Field X) or a symbol derived by use of a special grid for correlating doses and responses of less than 100% (when using any of Criteria 51 through 59). (See the special discussion, in Fields X and Y, of the CBCC Log-probit Grid.)

It should be noted that the two criteria, 20 (Threshold Dose) and 21 (Maximum Tolerated Dose) each describe a dose level which is related to a single, standard level of response. Ordinarily, this is expressed as a single dose level for which reason Fields M and N would correspondingly be coded

only with a single dose level. However, it is possible that as a result of several determinations using a number of organisms, a threshold dose or a maximum tolerated dose may be expressed as a range of doses, a given percentage of the organisms having the threshold or tolerance at one level, another percentage having the threshold or tolerance at a slightly different level, etc. In the latter case, Fields M or N should be coded to include both extremities of this range of threshold doses or maximum tolerated doses (double coding if necessary) and the Grid should be used to derive a Field Y rating as described in the specific directions and explanations for Fields W, X, and Y, Division 14 (paragraph 8) and Division 15 (paragraph 8).

17. Further consideration of double coding in Fields M and N; relations to double coding in other fields

The construction of a single line for several tests (when there is variation in the test dosage, yet the test results are so similar that they can all be coded by a single symbol in Field Y) is described in the preceding divisions. This coding procedure, which calls for double coding in Fields M and N with that single code symbol in Field Y, is in general the same procedure as used when duration of administration (Field P) or duration of action (Field U) is the test variation rather than the dosage level. In such a case, Field P or U is double coded with a single evaluation symbol in Field Y and all entries are punched on the same IBM card.

Occasionally, test data are encountered in which, in a series of tests, the variation in the tests is not just dosage size or just duration of administration, but variation in dosage size as well as duration of administration or duration of action, and the evaluation for two or more of these tests is expressed by a single symbol in Field Y. Since coders frequently attempt to double code the dosage fields and another field in the same line (Field P, U, or V, e.g.) and err in doing so, it will be discussed here briefly.

Observe first that when only one field is double coded, the subsequent interpretation of the line is uncomplicated, as follows: The test evaluation given in Field Y was the test result regardless of whether the larger or smaller of the two values coded in the double-coded field was used in the test method. (E.g., if Field N is double coded and Field Y is coded to indicate moderate activity [Symbol 5], that degree of activity resulted from any dose between the highest and lowest indicated by the coding in Field N.)

However, when two variables occur in a test method and when several of the tests give results that can be indicated by a single symbol in Field Y, if two fields are double coded to record the two variables, coding must permit the subsequent interpretation as direct and uncomplicated as in the example of the above paragraph. It is with this situation that the coder must exercise caution. The regulation which must be followed when two or more fields are double coded is explained diagrammatically below.

In considering the double coding of more than one field in a single line, the coder must deliberate upon the inter-relations of the entries for those fields to be double coded, as indicated by the statements of the diagram. (It is possible to write in code that 10-mg doses given hourly for 4 days will give the same test results [or at least test results coded by the same symbol in Field Y] as 100-mg doses hourly for 12 hours; it is not possible to punch this and retrieve it by the IBM machines used by CBCC and retain the strict association between each dose and its own period of administration.) The reasons for this procedure will be appreciated only through understanding that the IBM machine methods used by the CBCC will not allow any other procedure.

If double coding occurs in the two Fields, M and P,

Field M Column 46	Field P Column 51	Field Y Column 71
4	4	
		5
5	6	

it must mean that each duration in Field P is applicable to each dose in Field M--

4 ⟍⟋	4	
		5
5 ⟋⟍	6	

otherwise, two lines are necessary (or only one of these is selected for coding, according to the coder's judgment, with the other information in the language portion).

4	6	5
5	4	5

18. Symbols available for additional items of Fields M and N

Columns 46 and 48: Only Symbols 0 and 1 through 9 are permitted in these columns by the CBCC. This restriction is made to permit direct correlation between the dosage fields (Fields M and N) and the evaluation field (Field Y). By virtue of this limitation, the IBM zone punches were made available for specific purposes. (See Divisions 5, 6, 7, 8, 9, and 10). Having assigned special meanings to the zone punches, letter symbols can not now be used in this column in any case.

Columns 45 and 47: In Field M there are eleven scales, indicated by Symbols 1 through 9, A, and B. In Field N there are nineteen scales, indicated by Symbols 1 through 9 and A through J. Therefore, Symbols C through Z are available in Column 45 of Field M and Symbols K through Z are available in Column 47 of Field N for new scales.

19. File of coded biology data on IBM punched cards arranged according to symbols for dosage concentration and quantity

The CBCC has not established files of IBM punched cards arranged according to entries in Field M and by entries in Field N. Although searches for information from the files often involve sorting according to designated dosage limitations, this particular sort is almost never a primary sort, but secondary to having first selected specific actions or specified test organisms, etc., for which there are special IBM punched card files.

20. Double coding in Fields M and N

Fields M and N can be double coded according to the explanations of Divisions 15, 16, and 17. Any two symbols coded in Column 46 or 48 are both punched in that column on the same IBM card.

(1) DOSAGE FREQUENCY

(2) SEQUENCE OF ADMINISTRATION OF THE SECONDARY COMPOUND AND THE TEST COMPOUND

Organization

The frequency-of-dosage items of Field O have been limited to nine to which have been assigned only numerical symbols. This has permitted the remaining IBM punches (the three zone punches, 0, 11, and 12) to be used for a coding purpose distinct from frequency of dosage, namely, indicating the sequence of test compound and secondary compound administration.

General Use

Fields M, N, O, and P can be considered as a unit in that, together, they express the total amount of test compound administered during the test. (In Fields M and N are coded the size of the individual doses, in Field O is expressed the frequency at which the doses are given, and in Field P is indicated the period over which the doses are given at the frequency expressed in Field O.) The three fields are provided for dosage, rather than a single field, because any of the experimental factors, individual dose size, frequency of administration, and duration of administration, even though their significance may be minor in certain tests, are critical factors in many tests.

Besides its use for indicating the test compound dosage frequency, Field O is used for indicating the sequence of administration of test compound and secondary compound, when a secondary compound is involved. (See Divisions 7 and 8, below, and Division 3 of Specific Directions and Explanations for Field P, relative to this use of Field O.)

Thus, two types of information are coded in the same field (in a single column) and they may be both coded in the same line and both punched on the same IBM card. This double use of a single field, by which either or both of two entries may appear in the same IBM column, is distinct from "double coding". The latter expression, double coding, refers to the entry of two values of the same type of information--for example, two dosage frequencies, two test compound-secondary compound frequencies, or (in Field N) two dose ranges.

Specific Directions and Explanations

1. Suggested time ranges to be used in coding dosage frequencies

Some explanation is appropriate for the frequency-of-dosage definitions for Symbols 1 through 9. As with other quantitative values (in Fields M, N, P, U, and V), the definitions must be interpreted as encompassing ranges of time intervals, even though each is expressed in rather precise terms. For example, although "three times daily", if accomplished by exact timing of intervals, would imply an administration every eight hours, other routines are possible for a three-times-daily administration (e.g., daily at 7:00 a.m., 2:00 p.m., and 9:00 p.m., which would be a 7-7-10-hour series, or daily at 9:00 a.m., 1:00 p.m., and 5:00 p.m., a 4-4-16-hour series). Thus, within a 24-hour period, intervals may vary, rather than be precisely equal, for a "three-times-daily" administration schedule or for a "twice daily" schedule. In addition, the intervals may be such that the schedule doesn't fit precisely the definition for the terms "hourly" or "daily". For example, administration every 9 hours would mean administration of only two doses within a 24-hour period, yet the intervals are actually more nearly three times daily than twice daily. Similarly, administration every 3 hours is more nearly hourly than three times daily. The following scale is provided as an aid in determining which symbol to use when an administration schedule does not fit precisely the definitions of the code.

Symbol	Assigned time interval	Time interval range scale
3	More frequent than hourly	<45 minutes, but not continuous
4	1 hour	45 minutes through 4 hours
5	3 times daily	> 4 hours through 10 hours
6	2 times daily	>10 hours through 18 hours
7	One day	>18 hours through 36 hours
8	Every other day	>36 hours through 60 hours
9	Every 3 days or less frequently ...	>60 hours

2. Double coding of two frequency schedules or of two secondary compound-test compound sequences in two or more tests

Double coding is described and defined in Division 15 of the Specific Directions and Explanations Section of Fields M and N (as it applies to those fields). If the evaluations from two or more tests are so alike that they are coded by the identical symbol in Field Y and if the only variations in the two or more tests are the schedules of administration (Field O), all the schedules used for those tests may be coded in Field O in a single line and all punched on the same IBM card. Similarly, if the only variation between two or more such tests is the sequence of administration of test compound and secondary compound, the sequences of administration may be coded in a single line and all punched on the same IBM card. (See Division 5 of this section concerning the situation of variation of frequency during a single test.)

Double coding in Field O and another field, in the same line, is seldom possible. Thus, if Field O is double coded with two frequencies of administration (e.g., hourly and 3 times daily, Symbols 4 and 5), the dosage size (Fields M and N) and the duration of administration (Field P) must be the same for both frequencies of administration. For example, if the dosage size varies as well as the frequency of administration, it is impossible to indicate which of the doses double coded in Field M or N is related to either of the frequencies double coded in Field O. It is not possible, in other words, to indicate in one line that a large dose given at short intervals and a smaller dose given at longer intervals accomplish the same result; this can only be done by coding two lines. (See also Division 17 of the Specific Directions and Explanations for Fields M and N.)

3. Coding of ad libitum feeding

When the test compound is administered ad libitum, the CBCC codes Field O with the same symbol as for "continuous supply insured", Symbol 2. If, however, in ad libitum feeding, the total quantity of test compound consumed is determined and expressed as quantity per unit time, the quantity is recorded in Field N, the unit time is coded in Field O, and the total duration of treatment is expressed in Field P.

4. Distinction between use of Symbols 1 and 2

Symbols 1 and 2 are used to specify a single application of the test compound. This application technique may be designed to provide a continuous exposure of the organism to the test compound (Symbol 2) or the organism may be exposed to the test compound for only a very short period of time (Symbol 1).

Symbol 1 is used for those application methods exemplified best by oral administrations and by single simple injections (intravascular, intraperitoneal, etc.) which occupy only the time needed for swallowing or for puncture, injection of the test compound, and withdrawal of a syringe. Even in the case of special and tedious injections (certain intra-organal injections, e.g.), the time is considered negligible. The fate of the ingested or injected material thereafter is essentially dependent on the biological-chemical interaction; the compound may be quickly dispersed and eliminated, or it may be only very slowly eliminated, or it may selectively accumulate in one tissue. In any case, if the procedure of single administration did not provide for prolonged exposure of the treated test organism (or the treated anatomical part of the test organism) at the dosage level coded in Fields M and N, Field O should be coded with Symbol 1 and Field P will not be coded, since there is no significant duration of exposure guaranteed at the level indicated in Fields M and N.

When the test procedure involves a single application which provides for a prolonged exposure to the test compound at the dose level indicated in Fields M and N, the duration of exposure is considered significant and, if known, is coded in Field P. This application is indicated in Field O as

being continuous and is coded by Symbol 2. A continuous administration is exemplified by the method in which a regulated volume and concentration of test compound flows over a period of time into the venous circulation through a syringe fixed (i. e., by single application) in a vein. An administration is also continuous when bacteria, fungi, animal larvae, etc., are grown in or on a habitat or medium which has been impregnated with, dipped in, or painted with the test compound. An application of the test compound in a paste or ointment to plant or animal parts, when the concentration remains relatively constant over a considerable period of time, may also be properly considered as continuous and coded with Symbol 2 in Field O.

5. Two or more frequencies of administration during a single test

If the frequency of administration is varied during the period of a single test, there is posed the problem of deciding which of these frequencies to code, since only one can be coded. It would be convenient in such a case to have a series of columns for coding each frequency in sequence or at least a symbol for Column 49 which would represent frequency variance. Lacking these, the coder must be responsible for making the most intelligent choice relative to the specific situation, as in the similar situation in Fields M and N when the dosage size varies in a single test (see the first paragraph, Division 11, Specific Directions and Explanations, for Fields M and N). The legend of the series of frequencies should be included in the written abstract portion of Field O.

6. Persistence of residue data: definition; coding in Field U; coding in Field O

The expression, "persistence of residue", is used to refer to the length of the period over which a test compound, applied once to an environment or host, retains potency to produce a given specific action on a test organism. To determine persistence of residue, a series of exposures of the test organism (i. e., a series of tests) are made, separated by appropriate intervals, each being merely to determine whether the test compound residue is still capable of producing the action on the newly-exposed test organism after the period since the previous test.

This persistence of potency of a residue is not itself a biological action of a test compound, but is instead a specific characteristic of the chemical, related directly to, or representing, its physical properties. (The CBCC has not devised a code for physical properties. Such a code would include this duration of potency, a characteristic that would fall in the same category as "stability" of compounds, "stability in the presence of light", "resistance to oxidation", "boiling point", etc. Such properties are not recorded in Field T-2 as if they were specific actions nor is there any other special coding area provided for them.)

The CBCC has nevertheless made exception for indicating this one property, persistence of potency, inasmuch as its importance seems to justify it. From the data of tests demonstrating persistence, the CBCC extracts the information about the biological action demonstrated by the first exposure of the test organism to the test compound residue. (Data from only that first test are coded; information on the effectiveness of the test compound upon any subsequent exposures of the test organism to the same residue are not coded.) However, the entire period of time over which the residue was shown to be effective (i. e., persistence of the residue) is recorded in Field U (Column 66) of the same code line that records the data from the first exposure. When this information is recorded in Field U, Symbol * is always coded in Column 66 to indicate that the coding of that field is not duration of action in a single test, but is the period of persistence of a residue.

In a test demonstrating the action of a residue of the test compound (whether or not the test is one of a series demonstrating persistence of the residue), the test organism is ordinarily exposed to the concentration in the residue for a measurable period of time. Therefore, the administration is coded in Field O as being continuous (Symbol 2) and the duration of this exposure is coded in Field P. The time between the introduction of the test organism to the residue and the reading of the initial result is coded in Field V. (See also Field U, Specific Directions and Explanations Division 4.)

7. Sequence of administration of test compound and secondary compound

This second use of Field O is with Symbols 0, #, and * (IBM zone punches 0, 11, and 12). (Since these symbols can be used independently of the symbols for frequency of administration of the test compound [Symbols 1 through 9], the single column of Field O can contain both types of information. In other words, any of Symbols 0, #, or * can be coded in Field O along with any of Symbols 1 through 9.)

Either type of information may be double coded, if necessary (see Division 2), so that two or more of Symbols 0, #, or * can be double coded, two or more of Symbols 1 through 9 can be double coded, or both can be double coded, though the situation for which this would be necessary is improbable or infrequent.

8. Relationship between Fields O and P; the complication arising from Fields O and P having two uses

Field P is used primarily to express the duration of administration of the test compound at the frequency indicated in Field O. However, when coding data from tests involving a secondary compound, Field P is always used to indicate the time between administration of the secondary compound and administration of the test compound. If the two compounds are administered simultaneously, however, there is no intervening time and Field P is therefore freed for indicating any period of administration of the test compound. The following coding pattern will be observed accordingly.

When a secondary compound is administered prior to or after administration of the test compound and when, therefore, Field O is coded with either of Symbols 0 (test compound administered prior to secondary compound) or # (test compound administered after secondary compound), the time between administration of the two compounds is coded in Field P. If doses of the test compound are subsequently administered so that a frequency of administration of the test compound is also coded in Field O, the duration of administration can not be coded in Field P or elsewhere, but it must be recorded in the written abstract portion of Field P. If Field O is double coded with both Symbols 0 and # (see Division 2), the coder must use his best judgment as to which of the periods to code in Field P and which to include only in the written abstract portion of Field P. (In such a case, the two periods, corresponding to the two situations indicated by Symbols 0 and # in Field O, are apt to be nearly the same.)

When a secondary compound is administered simultaneously with the test compound and when, therefore, Field O is coded with Symbol * (test compound and secondary compound administered together), Field P is not coded, although if doses of the test compound are subsequently administered so that a frequency of administration of the test compound is also coded in Field O, the duration of administration is coded in Field P. If Field O is double coded with Symbols 0 and * or with Symbols # and *, Field P is coded with the time between administrations indicated by Symbol 0 or by Symbol #, as described in the preceding paragraph.

In summary: When Field O is coded with either or both of Symbols 0 or #, Field P expresses the time between administrations of test compound and secondary compound. When Field O is coded with only Symbol *, or only with any of Symbols 1 through 9, or with Symbol * plus any of Symbols I through 9, an entry in Field P expresses the duration of administration of the test compound.

9. Symbols available for additional items of Field O

Inasmuch as each of the three IBM zone punches have been given special meanings and can be used with any of the numerical punches (representing thereby two units of information), they can not be used in punching combination with numerical punches to form letters for symbols. Therefore, none of Symbols A through Z can be used in Field O as it is now designed, and all other available symbols have been used.

10. File of coded biology data on IBM punched cards arranged according to symbols for dosage frequency

No file of coded biology data in which Field O has been used has been established and arranged by Field O entries. The information coded in Field O is of such a nature that sorting for it is almost invariably subsequent to retrieval of information by specific actions, test organisms, test compounds, etc. (for which there are special IBM files); after the initial sorts by other code fields, the number of IBM cards is sufficiently limited to make efficient a simple mechanical sort or visual interpretation of dosage frequency.

11. Double coding in Field O

Double coding (with the restrictions noted in Division 8) is permitted in Field O. When Field O is coded with Symbol *, #, or 0 and also with one of Symbols 1-9, both symbols are punched on the same IBM card in Column 49. If more than one of Symbols *, #, and 0 are coded (double coding) or/and more than one of Symbols 1-9 are coded (double coding), all the symbols are punched on the same IBM card in Column 49.

DURATION OF TREATMENT
-or-
TIME BETWEEN ADMINISTRATION OF THE TEST COMPOUND AND A SECONDARY COMPOUND

Organization

As in the case of other quantitative values (e.g., values of Fields M, N, O, and Q), time values of Field P are not recorded literally (requiring three or more punched card columns), but are converted to one-unit code symbols by organizing the total range of time into limited ranges, each of which is represented by a code symbol. In the case of Field P, the most simple organization would have been by dividing time into 35 ranges for 35 symbols (26 letter and 9 numerical symbols) for a single IBM column or, if two IBM columns were used, by dividing time into many more than 35 smaller ranges. In either case, such a simple arrangement would have been a continuum of time values.

The actual pattern of organization, however, was determined by the fact that a test compound's activity may be evaluated on the basis of the duration of treatment. (Ordinarily, the less time the compound must be administered, the more efficacious can be considered the treatment.) Thus, a relationship exists between Field Y of the Biology Code (the field expressing evaluation of the compound's action) and Field P. Since Field Y expresses evaluations only in broad terms, using only Symbols 1 through 9, the Field P symbols used for correlation with Field Y have likewise been restricted, in the second column, to Symbols 1 through 9.

It was decided to incorporate into the pattern of organization of Field P some correlation to the type of biological action being tested. (The recording of a test compound's relative worth with respect to the action it has been demonstrated to produce is a persistent and difficult coding problem.) For this reason, the total range of time of Field P has been broken into several overlapping ranges, each succeeding one expressing time values in broader terms than the one preceding it. For example, the seventh total range (referred to in the Code as Scale 7) expresses time values as <6 hours to >32 days, whereas the sixth total range expresses time values at <45 minutes to >4 days.

The purpose in this, as suggested above, is to provide a means of fitting the coding to the field of chemical-biological research in which the test was conducted and to the evaluation as it was derived and expressed by the author. The reader is referred to the discussion of Fields M and N, particularly to Division 3 of the Specific Directions and Explanations section, where it is explained that in those coding fields no such breakdown of total ranges is made for the purpose of correlation with differences between chemical-biological research fields. If it were, each scale of Fields M and N (e.g., Scale 1 of Field M, ppm) would necessarily be broken into a number of overlapping ranges just as is total time in Field P. It may be questioned, then, whether the organization of Field P for the purpose of correlation to evaluation is justified when certain other coding fields of quantitative values, Fields M and N, have not been similarly organized. This can only be answered on the basis of the CBCC Code being an experimental one and subject to change. The pattern of Field P, as well as that of Field U, represents an effort to establish a coding relationship between any given field of chemical-biological research (insecticidal vs. plant growth regulation vs. enzymology, etc.) and the basis of evaluation (duration of administration, duration of action, etc.) of results from tests in that research field. Although the same has not been done in the case of Fields M and N, it must be recognized that in those dosage fields, the total range represented by any one scale and the division of the total range was not established in a purely arbitrary manner, but the scale was arranged to correspond to the field of chemical-biological research in which the unit of measure represented by the scale would be most appropriate and most apt to be used by an author. (See paragraph 5 of the Organization section of Fields M and N.)

Field P and Field U could each be reduced to a single continuous scale, while, in the reverse, Fields M and N could each be expanded so that each existing scale of those fields could be converted to a series of overlapping scales to be used selectively as the present scales of Fields P and U are now used. In adapting the CBCC Code, the patterns adopted in Field P (as well as Fields M, N, and U) will depend upon whether or not further emphasis is to be placed on attempts to express accurately test evaluations based on dosage size or time values, correlated with the chemical-biological research fields concerned.

General Use

Coding in Field P may be considered as one component of a group of three which, together, express the amount of test compound administered: The dosage size (Fields M and N), the frequency of administration of that dose (Field O), and the length of time the test compound is administered (Field P), at that dosage size and frequency.

Superimposed on this use of Field P is a second use, for the situation in which a secondary compound is administered in a test. In such a test, the test compound is usually administered only once and therefore a field is not frequently needed for expressing duration of treatment. Thus, under these circumstances, Field P is ordinarily free for this second use, the coding of the time between administration of the test compound and the secondary compound.

Specific Directions and Explanations

1. Selection of the scale to be used for coding duration of administration

The purpose in dividing total time into the several scales is explained in the section discussing organization of Field P. The coder will understand that the selection of a scale is left to his judgment. The scale should be used which seems the most reasonable choice relative to the field of chemical-biological research to which the test data belong, i. e., the scale that will allow the most exact coding of all data from that testing field. This is not always easy. Whether there is always only one scale most appropriate for any one situation might be questioned. It is probably more accurate to consider that for each testing situation certain scales of Field P are more appropriate than others, rather than to suggest that for every situation there is one most appropriate scale. Testing of compounds for molluscacidal activity or for antimalarial activity represents fields of chemical-biological testing for which Scales 1, 2, 3, and 4 might be easily seen to be inappropriate, since such treatment is ordinarily much longer than any of the periods in those scales, so a higher scale would be considered, probably Scale 7, though under some conditions Scale 6 or Scale 8 might be used for molluscacidal or antimalarial data.

In summary, an appropriate scale in Field P is:

(1) the scale that allows the most accurate statement of the duration of treatment and--

(2) the scale whose time values might reasonably be expected to encompass all durations of treatment typically used in testing in the field of chemical-biological research involved.

To illustrate the first of the above points, consider that to code a 6-minute duration of treatment, Scale 2 would not be the appropriate scale, because it could only be coded as being more than five minutes, which could be 6 minutes or 6 years. Scales 3 or 4 would be more appropriate scales for coding most accurately 6 minutes. To illustrate the second of the points, consider the observations made relative to antimalarial and molluscacidal tests in the paragraph above.

If the coder has little basis for judging appropriateness of a scale relative to the type of activity for which the test was run, the scale should be chosen on which the observed time falls on (or as near as possible to) the mid-point (Symbol 5 in Column 51). For example, if the duration of administration is 14 days and there is no other basis for selecting another scale, Scale 8 would be selected only because 14 days falls at the mid-point of the scale. In making a selection on this basis, another problem is sometimes encountered as illustrated by a time value of 7 days. In this case, the value is not at the mid-point of any scale and the question arises as to which scale to choose, Scale 7 or Scale 8, since 7 days is as near the mid-point of one as it is the other. In this case, when the scale is being selected only on the basis of proximity to the mid-point of a scale, the CBCC always uses the lower scale (in this case, Scale 7).

When data are reported in terms such as "several hours" (or as other comparably indefinite expressions of time periods), Scale A should be used.

If data from a single test are indefinitely reported as a range of time (e. g. , four days to two weeks), an average value (in this case, 9 days) will be coded. This occurs occasionally when the author describes a technique used in testing a series of compounds, and when he doesn't report the exact duration of administration for each test run. However, do not code an average for such a range unless the effectiveness, as coded in Field Y, is uniform over the total range.

2. Coding of the actual exposure time in Field P, regardless of the maximum exposure time characteristic of a special technique

Care must be taken in coding Field P when an action is observed before the end of a standard exposure period. For example, consider the technique for a standard screening test for toxicity. In this test, each test compound is administered daily for a maximum of seven days. If the test compound did not cause death at the dosage given, Field P should be coded with "seven days", but if death resulted on the fourth day, Field P should be coded with "four days". Consider, as a second example, a technique in which compounds dissolved in water are tested for their herbicidal effect on water plants by growing the plants for three days in the test solution and then transferring them to tap water for an additional four days of observation before an evaluation of their herbicidal effect is made. In coding the herbicidal effect, "three days" (exposure time) would be coded in Field P and "seven days" in Field V (time of evaluation). If, in addition, it is desirable to code production of chlorosis two days after removal to tap water, the coding in Fields P and V would be 3 and 5 days, respectively. However, if the chlorosis were produced two days after initiation of the test (i. e. , prior to the appointed time for transfer to tap water), "two days" would be coded in both Fields P and V.

3. Relationship between Fields O and P; the complication arising from Fields O and P having two uses

The two uses of Field P occasionally conflict. A thorough discussion of this will be found in the Specific Directions and Explanations section for Field O (Division 8) to which reference should be made. In brief, the information on time between administration of secondary and test compounds, when they are not administered simultaneously, is always given preference. In a test in which the test compound and secondary compound are not given simultaneously, and the test compound is subsequently administered over a measurable period of time (indicated by any of Symbols 1 through 9 in Field O), that duration of administration of the test compound can only be included in the written portion of Field P.

4. Symbols available for additional items of Field P

Inasmuch as the IBM zone punches have not been given special meanings in either column of Field P, letter symbols are available for use, except that in Column 51 the CBCC restricts time range coding to numerical symbols (i. e. , Symbols 1 through 9), to correspond to evaluation ranges in Field Y. The ten scales now in the Code are fairly exhaustive of time ranges expected in most chemical-biological tests. (Letters B through Z are available for any new scales needed.)

5. File of coded biology data on IBM punched cards arranged according to symbols for duration of treatment

No file of coded biology data in which Field P has been used has been established and arranged by Field P entries. Information coded in Fields M, N, O, and P is of such a nature that sorting for it is almost invariably subsequent to retrieval of information by specific actions, test organisms, test compounds, etc. (for which there are special IBM files).

6. Double coding in Field P

If the evaluations of two or more tests are so similar that they are coded by the identical symbol in Field Y and if the only variation in the two or more tests is the duration of administration (Field P), all the durations of administration may be coded in Field P in a single line (always by the same Field P scale, however, indicated in Column 50) and all punched in the same IBM card. (See the last paragraph of Division I for coding a variation or range during a single test.)

If the only variation in two or more such tests is the length of time between administration of the test compound and the secondary compound (indicated by Symbol 0 or # in Field O), all these periods of time may be coded in Field P and all punched in the same line.

FIELD P
Columns 50 and 51

As in the case of certain other fields (Fields M, N, O, and V), it is seldom possible to double code in Field P and another field in the same line. For example, if Field M is double coded (to indicate that the test evaluation would be nearly the same whether the test compound was administered at either of the higher or lower doses indicated), Field P can not be double coded (to indicate, e.g., that the test evaluation would be nearly the same whether the time between administration of the test compound and secondary compound was longer or shorter) unless each coded dose, administered after each of the coded periods, produced the same result. (This is also discussed, for combined double coding of Fields M or N and other fields, in Division 17 of the Specific Directions and Explanations for Fields M and N.) If Field P is double coded, therefore, it is improbable that Fields M, N, O, and V can be also double coded in the same line.

SIZE OF INOCULUM OR IMPLANT

Organization

In Field Q, symbols are assigned to nine ranges of numbers, the range increment (x10) being considered representative of typical inoculations and adequate for ordinary distinctions between tests differing in respect to inoculum size. The repetition of the list of symbols, expressing the definitions in a different way, is merely for convenience, since authors may express inoculum size in either terminology.

General Use

Field Q is used to record the number of individuals of the unicellular organism coded in Field E (e.g., Protozoa or Bacteria) or the number of cells of the cancer coded in Field E, contained in the inoculum or implant made to the host coded in Field J. The field is used also to record the number of individuals of any infective stage of a parasitic test organism coded in Field E, introduced into the host coded in Field J.

Specific Directions and Explanations

1. Coding in Field Q when the inoculum size is expressed as being within a range

Occasionally an inoculation is made in which the size is expressed only as being somewhere between an upper and lower limit; for example, an inoculum of "from 10^3 to 10^5 cells". Field Q must never be coded with two symbols representing the possible minimum and maximum size of such an inoculum, because such coding would imply that two separate tests had been run, one with a small inoculum, the other with a large inoculum (as explained in Division 6). Instead, Field Q would be coded with an average. (In the example given, 50,500 cells would be coded, using Symbol 5.)

2. Definition of the entry in Field Q

The definitions for symbols of Field Q are exclusively in terms of the total number of cells or individuals of each inoculum or implant; therefore, a Field Q entry is never in terms of the number of cells or individuals per unit of volume or weight of the suspending medium. If data are given in terms of numbers per unit volume or weight of implant or inoculum and the total number of cells or individuals inoculated or implanted can not be calculated, no entry is to be made in this field.

Development of a population of implanted organisms, subsequent to the implantation depends on the test organism species involved. Certain organisms, notably many helminths, can not complete their life cycles within the host into which they are inoculated and consequently the population resulting from the inoculation and the degree of severity of the associated pathology is limited to the number of individuals introduced. Other organisms (Bacteria and Protozoa) can reproduce indefinitely within the host and the final population and severity of an associated pathology is limited only by natural tissue barriers or immune factors in the host or by death of the host. The size of the population of test organisms, such as most Bacteria or Protozoa, at the time of treatment, or the size that would be expected at the time of evaluation, if there had been no treatment, is dependent on the two factors, size of the inoculum and length of time from inoculation. The CBCC has not required the coder to be able to distinguish the two situations, thus no code symbol is provided for indicating that the inoculum size is the same as the final population size, as opposed to its being less than the final size. Thus, there is no indication in Field Q as to whether the inoculum size is finite (just as when six test organism individuals, not in a host, are used in a single test) or whether it represents only a beginning population which can reproduce to an indefinite size. The interpreter of the code line, however, must be able to interpret the coding of Field Q with respect to a knowledge of the test organism's capacity for reproduction in the host (i.e., its life cycle) and with respect to the number of organisms normally expected after a given period of time.

3. In vitro experiments

Field Q may be used to record the inoculum size for in vitro experiments as well as in vivo experiments.

4. Symbols available for additional items of Field Q

Since none of the IBM zone punches have been used for special purposes, any of Symbols A through Z are available for additional use in Field Q. However, as the size ranges are now, no further symbols are needed for that purpose.

5. File of coded biology data on IBM punched cards, arranged according to symbols for inoculum size

The CBCC has no file of coded biology data arranged by Field Q symbols, because of the improbability of beginning an information search by looking for inoculum size.

6. Double coding in Field Q

If the evaluations of two or more tests are so similar that they can be coded by the identical symbol in Field Y and the only difference between the two or more tests is the size of the inoculum, all the inoculum sizes may be coded in Field Q and all punched on the same IBM card. This is referred to as double coding. For example, if the evaluation coding is the same regardless of whether the inoculum is 10, 50, or 100 cells, Field Q is coded with Symbol 2; whether the inoculum is 10, 100, or 500 cells, Field Q is coded with Symbols 2 and 3; whether with 100, 1000, or 10,000 cells, Field Q is coded with Symbols 2 and 4. (See Division 1.)

TIME OF TREATMENT
RELATIVE TO:
(1) INOCULATION
(2) TUMOR IMPLANTATION
(3) SENSITIZATION
(4) INCITATION OF NON-INFECTIOUS PATHOLOGY

Organization

As with all fields of the CBCC Biology Code concerned with quantitative data, each symbol of Field R designates a time range. As the symbols are listed in the Code, four groups can be recognized, according to the sequence of the administration of the test compound and the infection, implantation, etc.:

1. Test compound and infection, etc., administered at the same time--or essentially at the same time (within an hour of each other). (Symbol 1)

2. Test compound administered after the infection, etc. (Symbols 2 through B)

3. Test compound administered before the infection, etc. (Symbols C through L)

4. Test compound administered before and after the infection, etc. (Symbol M)

General Use

The time between implantation, inoculation, sensitization to the test compound, infection, etc., and the administration of the test compound is indicated in this field, when the time is relevant and important to the test.

Time values coded in Field R are those between administration of the test compound and:

1. Implantation of a tumor (coded in Field E).

2. Inoculation of a host with the cells or individuals of an infective stage of a pathogenic test organism coded in Field E.

3. A subsequent dose of the same compound administered to determine sensitization by the primary dose. Thus, Field R may be used to code time between the administration of an initial dose given experimentally as a sensitizing dose (or as a dose which reduces tolerance) and the subsequent dose, when coding the sensitive response to the second dose (i. e., when not coding sensitization or tolerance reduction [Symbol 58 or a symbol of the 51-- series], but indicating with Symbol 6 in Field G that the organism has been pretreated to account for the sensitivity resulting in the response coded in Field T at the dose administered). See the section on Specific Directions and Explanations for Field G, Division II, Subdivision A, Part (1).

4. The inciting of a specific non-infectious pathological state (coded in Field E) to be treated with the test compound. (This inciting of a non-infectious pathology is never coded in Field G in which could be coded, in this situation, only pretreatments or conditions other than the pathology to be experimentally treated.)

Field R is not used to indicate the time interval between administration of the test compound and the secondary compound; that information is coded in Field P.

Specific Directions and Explanations

1. Time to be coded when the test compound is administered PRIOR to a SINGLE implant

If the administration of the test compound is by multiple application and the total treatment with the test compound is prior to implantation, inoculation, etc., the time interval coded in Field R is the period between the last administration of the test compound and the implantation.

If the administration of the test compound is by single application and the treatment with the test compound is prior to implantation, inoculation, etc., the time interval coded in Field R is the period between the application of the test compound and the implantation. If the test compound is administered continuously for a period prior to implantation, the interval coded in Field R is the period between the end of the administration of the test compound and the implantation. (If the test compound is administered continuously up to the time of implantation, Field R must be coded with Symbol 1.)

2. Time to be coded when the test compound is administered AFTER a SINGLE implant

If the administration of the test compound is by multiple application and the treatment with the test compound occurs after implantation, inoculation, etc., the time interval coded in Field R is the period between the implantation and the first application of the test compound.

If the administration of the test compound is by single application and the treatment with the test compound occurs after implantation, inoculation, etc., the time interval coded in Field R is the period between the implantation and the application of the test compound. If the test compound is administered continuously for a period after the implantation, the interval coded in Field R is the period between the implantation and the beginning of the administration of the compound. (If the test compound is administered continuously beginning at the time of implantation, Field R must be coded with Symbol 1.)

3. Time to be coded when the test compound is administered PRIOR to MULTIPLE implants

If the implantation, inoculation, etc., is multiple and the administration of the test compound is prior to the implantation, the time interval coded in Field R is the period between (1) the last dose (when multiple doses of the test compound are given) and the initial implantation, or (2) the single dose and the initial implantation, or (3) the end of a continuous administration and the initial implantation.

4. Time to be coded when the test compound is administered AFTER MULTIPLE implants

If the implantation, inoculation, etc., is multiple and the administration of the test compound is after the implantation, the time interval coded in Field R is the period (1) between the last implantation and the initial dose (when multiple doses of the test compound are given), or (2) between the last implantation and the single dose, or (3) between the last implantation and the beginning of continuous administration.

5. Symbol 1

Symbol 1 is used to specify the administration of the test compound at the same time that implantation, inoculation, etc., occurs. This symbol is also used when the administration of the test compound occurs within an hour before or after implantation, inoculation, etc. Although time periods less than one hour might have been given symbols, they are seldom of sufficient significance to justify it. When the time period is one hour or more, the other code symbols are used.

6. Instructions for miscellaneous irregular situations

If data are indefinitely reported (e.g., ".... treated 4 days to 2 weeks after implantation..."), code the symbol that represents the average value of the reported range. Record the entire range in the written abstract of the field.

When an author indicates only that implantation, inoculation, etc., was on the "day of the last dose" (in cases of multiple doses of the test compound), without specifying whether the time between the last dose and implantation was less than or more than an hour after the last dose, use Symbol C. In the same way, when it is known only that implantation, inoculation, etc., was on the "day of the first dose of the test compound" or was "immediately after", use Symbol 2.

In the case of a single or continuous administration of the test compound, if the author only states that the test compound administration was "on the same day" as the implantation, inoculation, etc., without specifying which operation was performed first, use Symbol 1.

When the author states that treatment is administered "on the day following" (or "prior to") implantation, etc., there is posed the question as to whether the time interval was greater than, equal to, or less than 24 hours. Symbol 3 (or Symbol D in the case of "prior to") is to be used in these cases merely for consistency, since Symbols 2 and C are used for coding the expression "on the same day".

7. In vitro experiments

Field R may be used for indicating time between time of treatment and time of inoculation of in vitro tests as well as in vivo tests.

8. Symbols available for additional items of Field R

Inasmuch as the IBM zone punches have not been assigned for special purposes in Field R, any of the presently unused letters can be used as symbols (i. e., N through Z), although it seems probable that the time periods already designated in the field are adequate.

9. File of coded biology data on IBM punched cards arranged according to symbols for time periods of Field R

The CBCC has not established a file of coded biology data arranged by Field R symbols because of the improbability of beginning an information search by looking for inoculation-treatment relationships of tests.

10. Double coding in Field R

When the evaluations of two or more tests are so similar that they can be coded by the identical symbol in Field Y and the only difference between the two or more tests is the period between implantation, inoculation, etc., and administration of the test compound, all the time periods may be coded in Field R in one line and all punched on the same IBM card. This is double coding. Double coding in Field R has restrictions, however; IT IS POSSIBLE ONLY IF THE SYMBOLS DOUBLE CODED ARE NUMERICAL, SYMBOLS 1 THROUGH 9. The IBM procedure will not permit double coding of two letter symbols or a letter and numerical combination.

FIELD S-1
FIELD S-2
FIELD S-3
Columns 54, 55, and 56

ROUTE AND MANNER OF ADMINISTRATION OF:

(1) INOCULUM OR IMPLANT (FIELD S-1)

(2) SECONDARY COMPOUND (FIELD S-2)

(3) TEST COMPOUND (FIELD S-3)

Organization

Although each of these three coding fields is used for recording a unique aspect of chemical-biological tests, basically a single list of items serves to provide symbols for all three. Since only a single IBM column has been provided for each of the fields, only 35 symbols are available. (38 symbols might be regarded as being available, if the 0, 11, and 12 zone punches, used alone, were assigned unique Field S meanings.)

The arrangement of the items is arbitrary except that, when the list was compiled, those bearing similarities to each other were generally listed together.

Because certain items are not equally appropriate for all three fields, those symbols are given two or more definitions and where these multiple definitions occur, there is designated by each to which of the three fields, S-1, S-2, or S-3, its use is restricted.

General Use

FIELD S-1

This Field (Column 54) is used for coding the route and manner of administration of the test organism or tumor (specified in Field E), as an inoculum or implant, to the host, living or non-living, specified in Field J. The size of this inoculum or implant (i.e., the number of individuals of the test organism or the number of tumor cells, when this is estimated) is coded in Field Q.

FIELD S-2

In this field (Column 55) is coded the route and manner of administration of a secondary compound (specified in Field D) to the test organism or to the host (either a living or non-living host)--when this secondary compound is administered in the identical experiment in which the test compound is administered so that the interaction of the two compounds on the organism is evaluated (antagonism, synergism, or additive effect, Symbols 8, 9, and C of Field T-1). (Field S-2 could be used when Symbol A [simulation] is coded in Field T-1, if the route of administration of the secondary compound simulated were stated by the author, even though the administration of the secondary compound is not in the same test as that of which the results are being coded.) In other words, Field S-2 is not invariably used when there is an entry in Field D, but only under the circumstances just described; to be specific, it is not used when the entry in Field D is merely a standard of comparison or when it is a compound whose metabolic fate is affected by the test compound.

When a compound is coded in Field D as a standard whose action is compared to the test compound's action, it would be assumed that that standard, if it were truly eligible for comparison, had been administered (in those tests demonstrating its action) by the same route and manner as the test compound (in the test being coded) or that any difference in the routes of administration of the two compounds had no significant effect on the outcome of the tests of the two compounds. Therefore, since there is no need for such distinction, no provision has been made in the CBCC Biology Code, in Field S-2 or elsewhere, to indicate the route and manner of administration of a standard compound.

FIELD S-3

Field S-3 (Column 56) is used for coding the route and manner of administration of the test compound to the test organism or, if Field J is coded, to the host. In chemotherapy studies, when the test organism, tumor, or pathology (in Field E) is always in a host (Field J), it follows that, under those conditions, the coding in Field S-3 ordinarily describes administration of the test compound to that host. In such tests, if the administration is actually directly to the test organism or tumor rather than directly to the host coded in Field J, the coding of Field S-3 will apply to the test organism. Unfortunately, the CBCC coding of Field S-3 can not distinguish this fact and only by the general sense of the Field S-3 entry and by reference to the written abstract for Field S-3 can it be distinguished that the route coded refers to direct administration to the test organism or tumor. This is discussed also in Division 2 of the Specific Directions and Explanations for Field S-3. (Three of the items of Field S-3, Symbols J, M, N, and R, invariably imply the test organism's being in or on a non-living host to which the test compound is administered and which is always recorded in Field J; i. e., Symbols J, M, N, and R are restricted to reference to Field J by their definitions, so with these symbols there is no question as to whether the Field S-3 coding refers to the test organism or tumor in Field E or to the host in Field J.)

Specific Directions and Explanations

FIELD S-1

1. Tumor transplants

In cancer studies, a tumor transplanted into another animal is commonly introduced subcutaneously. If the author has not specified its transplant location as being elsewhere, the CBCC assumes it is subcutaneous and codes it with Symbol 8.

2. Relationship of Field S-1 with Fields H-1, H-2, and I

Field S-1 is not conceived as having a direct relationship to Fields H-1, H-2, and I. Although most frequently the site of administration of an inoculum (Field S-1) is also the site at which the inoculum (the test organism or tumor) establishes (Fields H and I), it is not invariably the case. Fields H-1 and I are always used for coding the location of the test organism or tumor at the time of the test, when a host organism is coded in Field J, and never for coding the site of administration of the test organism or tumor; if the site of administration of the inoculum or implant (the test organism or tumor) is identical to the location of the test organism at the time of the test, it is only coincidental. Neither is Field H-2 used for coding sites of administration of inocula and tumors, but only for coding structures as described in the section discussing Field H-2.

FIELD S-2

1. Use of Field S-2 is restricted to secondary compounds with which the test compound interacts, as signaled by certain symbols of Field T-1

This has been explained in the section on General Use of Field S-2, above. When Symbol 8, 9, or C is used in Field T-1, Field S-2 can be used; otherwise, Field S-2 is always to be left uncoded.

2. Secondary compounds can be administered to hosts as well as to test organisms; use of Field S-2 when Field J is coded with a host

Inasmuch as the test compound may antagonize, synergize, or have an additive effect on the therapeutic activity of a secondary compound, Field S-2 may be used when Field J is coded with a host organism--or even with a non-living host (e. g., Symbols J, M, and N of Field S-2). Thus, whenever Field J has an entry, any coding in Field S-2 is to be interpreted as being the route or manner of administration of the secondary compound to the host coded in Field J. Just as the test compound may in an occasional test be applied directly to the test organism even when it is on a host (coded in Field J), so is it possible that the secondary compound might be administered directly to the test organism when the test organism is on a host coded in Field J. Coding of Field S-2 can not distinguish, any more than

can coding of Field S-3, whether the test organism or the host organism is referred to by the route indicated. (See the section on General Use of Field S-3.)

3. Relationship of Field S-2 with Fields H-1, H-2, and I

Since Fields H-1 and I always are used to code the specifically responding structure of the test organism (when Field J is not coded with a host organism) or are used to code the site of the pathogen or pathology as coded in Field E (when Field J is coded with a host organism), those anatomy fields can not be used specifically to indicate the structure serving as the route of administration of the secondary compound. Neither can Field H-2 be used for this purpose, because it is reserved for describing the site of administration of the test compound, if this site is not the same as the site of response and if Field H-2 is not otherwise used. (See the description of Field H-2.)

FIELD S-3

1. Relationship of Field S-3 and Fields E and J

The use of Field S-3 is described above in the section on General Use. When Field J is not coded, a code entry in Field S-3 represents the route and manner of administration of the test compound to the test organism in Field E. When Field J is coded, a code entry in Field S-3 always represents the route and manner of administration of the test compound to the host organism or inanimate host in Field J, unless the written abstract of Field S-3 indicates that administration was essentially directly to the test organism even though a host is coded in Field J, as described in the last paragraphs of the next Division.

2. Relationship of Field S-3 and Fields M and N and the relation of each of Fields S-3 and Fields M and N to Fields E and J

The use of IBM 11 and 0 zone punches in Fields M and N (Code Symbols # and 0) is described in Divisions 5, 6, 7, 8, and 9 of the Specific Directions and Explanations of Fields M and N.

The IBM zone punches in Columns 46 and 48 do not alter the meaning of the coding in Field S-3. In Field S-3 is coded the technique of administration (i. e., route and manner). The zone punches of Fields M and N designate to which of two or three biological units (the host, or the test organism, or the responding organ or tissue) the test compound was exposed at the dose level coded in Fields M and N, regardless of the technique (route and manner) of administration.

For example, with the 12 zone punch (Symbol #) in Column 46 or 48, and with Field J coded, the dosage is the amount or concentration to which the test organism was exposed rather than the dosage administered to the host organism. This, however, is not synonymous with saying that the technique of administration (route of administration) has been likewise altered; in the example above, the actual route of administration (Field S-3) might have been directly to the host (Field J), in spite of the fact that the final concentration, as coded in Field M or N was determined as being the one to which the test organism was exposed, after distribution through the host. The zone punches in Columns 46 and 48 should not be considered to infer the actual route of administration which is coded only by Field S-3. In view of the foregoing, the coding in Field S-3 should follow the explanation as given above in Division 1, so that it describes only the technique of administration of the test compound. For example, aphids (Field E) on the leaves of rooted willow branches (Field J) were exposed to the test compound at Z ppm in the leaves (Field M, coded with Symbol #) when application was to the branches at 110 x Z ppm as a water solution in which the branches were placed (Field S-3, Symbol D). In this example, the route of administration (as coded in Field S-3) was to the host, in spite of Fields M and N indicating (by Symbol #) that the coded dosage was that to which the test organism was exposed.

If there is an entry in Field J and the test procedure describes the administration as being actually directly to the test organism, the CBCC Code has no way of coding this distinction specifically in Field S-3; it must, however, be adequately explained in the written abstract of Field S-3. Consider the following three situations for illustration: (1) the application of a fumigant or a spray of the test compound (Field S-3, Symbol J or K) at X ppm to aphids (Field E) on leaves of willow branches (Field J); (2) the application of the test compound at X ppm directly onto the abdomen (Symbol G of Field S-3) of a tick (Field E) whose forebody is buried in the skin of a dog (Field J), or (3) the direct exposure of ectoparasites (Field E) on a fish (Field J) to the test compound at X ppm in the water (Symbol N of

Field S-3). In all of these procedures, Field M would be coded with Symbol #, indicating that although a host was involved, the test organism was exposed to the dosage as coded in Field M; however, none of Symbols K, G, or N of Field S-3 explains (1) that the test compound was applied to the external surface of the aphids (and only coincidentally to the external surface of the willow leaves), or (2) that it was not applied to the abdomen of the dog, or (3) that it was applied to the habitat of the ectoparasites (and only coincidentally to the habitat of the fish). In such cases, the coder must always explain in the written abstract of Field S-3 this route of administration as being directly to the test organism rather than to the host of Field J.

3. Relationship between Fields S-3 and Field H-2

Of the uses for Field H-2, one relates particularly to Field S-3 (listed as Use #3 in the section on General Use of Field H): the gross anatomical site of administration of the test compound, when the site is other than an organ specifically responding in Field H-1, can be coded in Field H-2, provided Field H-2 is not otherwise used and if the coding in Field S-3 does not adequately designate the specific route. This use of Field H-2 is discussed in detail in the section on Specific Directions and Explanations (Divisions 2 and 3) for Field H. Briefly, certain symbols of Field S-3 adequately indicate the site of application and, when they are used, Field H-2 need not be coded with the site of application under any circumstances: Symbols 0, 1, 2, 6, 9, A, H, J, K, L, M, N, Q, R, T, U, V, W, X, and Y. The other symbols of Field S-3 represent routes which do not include in their definitions specification of an anatomical site and it is to supplement the definitions of these that Field H-2 can be used: Symbols 3, 4, 5, 7, 8, B, C, D, E, F, G, I, Ø, P, S, and Z. Ideally, a separate coding field (i. e., other than the field used to supplement coding in Fields G and L) would be provided for this supplementary coding to Field S-3, but the CBCC decision to use a single field (Field H-2) for both uses was based on the belief that both of those uses for Field H-2 occurred with sufficient infrequency that conflicts between the two uses would be correspondingly rare and that the significance of this small number of conflicts did not justify reserving another three IBM punched card columns for a special anatomy field to supplement Field S-3, when it was so important for efficiency to restrain the entire coding area to a single IBM punched card. Unfortunately, as is often the case when two uses are assigned to a single coding field, code entries in Field H-2 can be interpreted only by consulting the coding in Fields G, L, S-3, and H-1, as explained in Division 3 of the Specific Directions and Explanations section for Field H.

In the process of retrieving from the coded files data on tests in which a specific organ is treated with the test compound, the file search must include sorting in Field S-3, as well as in Fields H-1 and H-2.

4. Manners of application; Field S-3 and Field A distinctions

Field S-3 distinguishes in its descriptions manners of application to the several routes. The route and manner of application are often intimately linked in a given technique, so that actually Field S does not code two items of information (a code symbol for a route, as distinguished from a code symbol for a manner), but only a single item (the route which by its nature frequently restricts the manner, both being described by a single symbol). The manners of application described in Field S are limited: injection and implantation, insertion in the alimentary tract, perfusing through an organism or organ, and placing on the organism surface (by any of several mechanical means: rubbing, painting, brushing, dripping, spraying, washing, immersing, dipping, fumigating, etc.). These several manners of application, combined with selected specific anatomical parts (routes), make up the items of Field S, describing the more common techniques of application. Observe that the manners of application just mentioned are not synonymous with nor do they include the description of the state of the compound (e. g., liquid, solid, gas, as a continuous [undispersed] mass, or separated into particles to be discontinuous [i. e., dispersed as a suspension or emulsion, dust, spray, mist, etc.]). These states are coded only in Field A for the test compound, never in Field S-3, even though they may seem in some cases to be coded in Field S-3: certain manners and routes (e. g., Symbol J) are restricted to a single state of the test compound and the implication of that state is so strong, therefore, that Field S-3 appears to be coding the state. This distinction between Field A and Field S-3 is discussed also in the section on the General Use of Field A.

5. Symbols available for expansion of Fields S-1, S-2, and S-3

FIELDS S-2 AND S-3

All of the items of the Code are applicable to Fields S-2 and S-3 and there are no further symbols available for new routes except that the IBM 11 and 12 zone punches might be used alone for two new items.

FIELD S-1

Several of the items of the common Code list for Fields S-1, S-2, and S-3 are not ordinarily applicable for describing the administration of inocula. In particular, Symbols C and M have been designated in the Code as not being used in Field S-1. Thus, Symbols C, M, and the IBM 11 and 12 zone punches are available for additions to Field S-1.

6. File of coded biology data on IBM punched cards arranged according to symbols for routes of administration

The CBCC has established no separate files of biology data arranged by entries in Field S-1, S-2, or S-3.

7. Double coding in Fields S-1, S-2, and S-3

If more than one route of administration of inoculum or implant, secondary compound, or test compound (Fields S-1, S-2, and S-3, respectively) have been employed and the results of the tests using the different routes are so similar that the coding for the tests would be identical except for the entry in Field S-1, S-2, or S-3, both routes can be coded in that field to accommodate both tests in a single code line. This coding of two or more tests in a single line is referred to as double coding. HOWEVER, double coding in these three fields is possible only if the code symbols for both of the two routes are numerical, i.e., any of Symbols 0 and 1 through 9; if one or both of the routes is coded by a letter symbol (Symbols A through Z), a separate code line must be constructed for each test using a different route of administration. If Field S-1, S-2, or S-3 is double coded with more than one of Symbols 0 and 1-9, both or all of the coded symbols are punched on the same IBM card in the column for the field.

ACTION OF THE TEST COMPOUND

Organization of Field T

This field is divided into three areas or sub-fields (Fields T-1, T-2, and T-3) in the same way that the general area for coding the administered dosage is divided into four areas (Fields M, N, O, and P). Fields T-1, T-2, and T-3 are assigned one, four, and three coding columns (i. e., IBM punched card columns), respectively.

The three areas are designated as:

Specific Action (Field T-1)

Specific Biological State, Quality, or Process Acted on or Caused (Field T-2)

General Category of Effect; Practical Application (Field T-3)

General Use of Field T; Distinctions between General Uses of Fields T-1, T-2, and T-3

In this area is coded the biological response--in other words, a description of the chemical action on the organism. The first of the three subsidiary coding areas of Field T, Field T-1, is used to describe the exact action and is therefore referred to as the field for coding specific action. The second, Field T-2, is used for coding the specific biological state, quality, or process acted on or caused. Finally, Field T-3 is used to re-state the information coded in Fields T-1 and T-2 in terms of a general category of action.

In describing responses of biological organisms to chemicals--in other words, actions of test compounds on biological organisms--it will be noted that the expression of biological response (chemical action) always consists of two components, essentially a verb and an object (considering the test compound as being the subject of the statement of the test result). For each of these two components of the statement of biological response, a separate code area has been established, Field T-2 for the object (i. e., the state, quality, or process) and Field T-1 for the verb (i. e., the action of causing or affecting the state, quality, or process). Field T-3 supplements Fields T-1 and T-2 in that it defines the chemical action in terms of a general category of effect and practical biological application. Examination of items of Fields T-3 and T-2 will help clarify the distinctions.

Fields T-1 and T-2 should be regarded as a coding unit, the entry in each of the two fields being essential to a complete statement of action of the test compound (i. e., a complete statement of the response of the organism). Field T-3 is then a second coding unit, in which the chemical action (biological response) is re-stated in another, more general way. In programs of coding chemical-biological information which are of a considerably more restricted nature than that of the CBCC, it is conceivable that one of the units, (1) T-1 and T-2 or (2) T-3, could be eliminated.

SPECIFIC ACTION OF THE TEST COMPOUND ON THE BIOLOGICAL STATE, QUALITY, OR PROCESS CODED IN FIELD T-2

Organization

Twenty-five items have been listed and assigned code symbols in Field T-1. In constructing this list, the arrangement of the test compound actions has followed no special pattern.

General Use

Field T-1 is used to describe the test compound's action on the biological state, quality, or process coded in Field T-2 (or the action for which the compound is tested, even though the compound proved inactive). This general use of Field T-1 is further distinguished in the previous section discussing Field T as a whole.

Specific Directions and Explanations

1. Relations of Field T-1 to Field T-2

None of the items of Field T-1 represents an independently complete code statement. Examination of the terms defining symbols of Field T-1 will make clear that the Field T-1 entry must be accompanied by an entry in Field T-2 to form a complete code statement of the test compound's effect on the biological system or of the test organism's effect on the test compound. EVERY LINE OF CODED BIOLOGY DATA DEMANDS AN ENTRY IN BOTH FIELD T-1 AND FIELD T-2.

2. Action of the test compound on the biological system vs. action of the biological system on the test compound

Most of the terms of Field T-1 describe actions of the test compound on the biological system to which it has been administered. Certain tests, however, reveal the fate of the chemical itself instead of, or in addition to, the organism's specific response to it. For example, the biological system may store the compound, absorb it, alter it, etc. The terms of Field T-2 which describe these actions on the test compound are indicated by Symbols F9B, FAB, FBB, FGB, FIB, and any of the Symbol series FE-- and FF-B.

With any of the Field T-2 terms above (coding the action of the biological system on the test compound), Field T-1 is coded with Symbol 7. When used with these Field T-2 terms, Symbol 7 represents the term "undergoes" or "is", indicating the test compound's being acted on. With all other Field T-2 terms, Symbol 7 represents "causes", "produces", "induces", etc.

3. Field T-1 coding is NOT influenced by the test result being NEGATIVE

In collecting and recording chemical-biological data for future retrieval and study, it is as important to code specifically those actions which test compounds have been demonstrated unable to perform as it is to code those which test compounds have been demonstrated capable of performing. Therefore, when a test is run specifically to determine whether a chemical will perform a given action (or whether the chemical will be altered or otherwise affected in a given way by the test organism) and the chemical proves to be inactive (or to be unaffected by the test organism), Field T-1 can not express the fact that the specific action was not produced (or that the test compound had not been affected by the test organism). The code statement of Field T (including Field T-1) is always positive; if the data are negative, the negation of the Field T statement is accomplished by code only in Fields X and Y.

In Division 5 below, a slight variance in coding of Field T-1 for special negative data is discussed.

4. Field T-1 coding IS influenced by the test result being the REVERSE of an action for which the compound was tested

When a test compound has been administered in an effort to induce or affect in a given way a specific biological condition or process of Field T-2, the compound may prove to do the reverse (e. g., it prevents instead of induces or it decreases instead of increases the state or process in Field T-2). In this case, Field T-1 must be coded to record the action actually demonstrated; subsequently, it would be meaningless to construct a second line in which Field T-1 would be coded with the action for which the test was made and negate it by coding in Fields X and Y.

5. Coding of Field T-1 when a compound is tested for action on a specific biological state or process (coded in Field T-2), and the following factors all apply: (1) the state or process in Field T-2 is one that might be affected in either of two opposing ways, (2) the compound proved inactive, and (3) the author does not state for which of the two opposing actions the compound had been tested

Under these conditions, the CBCC avoids coding arbitrarily the compound's failure to accomplish one or the other of the two possible effects on the condition or process coded in Field T-2. Instead, both are coded. In essence, this would involve two biology code lines, one with Field T-1 coded with one action (e. g., increase), the other with Field T-1 coded with the opposing action (e. g., decrease); in actual practice, however, the CBCC conserves space and coding time by combining the two lines, accomplished by coding both actions in Field T-1 in the same line.

An exception to combining these two lines into one must be made in the case of the specific states indicated by Symbols of the two series, 171- and 161-, of Field T-2 (the number of pathogenic organisms having been diminished or increased). The association of alteration of the number of organisms with improving or exacerbating an infectious pathology necessitates defining those Field T-2 symbols as either being a state of diminished numbers of organisms or of increased numbers of organisms and Field T-1 is consequently coded with Symbol 7 to indicate that the state of diminished or increased numbers has been "caused". Since Field T-2 can never have more than one entry, two separate lines are necessary for this.

It might be pointed out here that when the author reports the test compound as having no effect and in addition does not indicate any specific biological state or process that was being treated or initiated (so that there is no specific entry for Field T-2), Field T-1 can be coded only with Symbol 0. (See Division 18 below.)

6. Symbols 1 and 2; quantitative change or change of rate (exclusive of total abolishment or prevention) of the biological state or physiological process coded in Field T-2

These symbols are each given two meanings, though the sense of increase is implicit in both of the definitions for Symbol 1 and the sense of decrease is implicit in both of those for Symbol 2.

Symbol 1: (a) increases
(b) accelerates
Symbol 2: (a) decreases
(b) slows

Thus, these two symbols can be used for coding the action of the test compound in increasing or decreasing size, number, or degree (e. g., increasing or decreasing the number of fruits [Field T-2, Symbol 191], nuclear size [Symbol 225], number of blood cells [Symbol 851], organism weight [Symbol 2A1], prothrombin time [Symbol 8731], or circulatory rate [Symbol C6]), which represents a quantitative effect only. However, the symbols are used also for coding the action of the test compound in increasing or decreasing the rate of any physiological process which is not defined in Field T-2 as a rate (e. g., accelerating or slowing the alteration of the test compound [Field T-2 Symbol series FE--], spiracular movement [Symbol B2], sol-gel transformation [Symbol 833], regional growth [Symbol 2A4]).

There might be some advantage to having symbols unique from Symbols 1 and 2 for distinguishing in Field T-1 that the action is one of altering a rate of a process rather than being one of alteration of number, size, or degree; this would permit clarifying the situation when certain biological conditions or processes are defined by Field T-2 terms which are somewhat ambiguous in this respect. For example, Symbol 1 of Field T-1, when coded with Symbol 261 of Field T-2 (seed germination), may indicate that the number of seeds germinated was increased or that the time (speed) of germination was shortened; a unique Field T-1 symbol for "increase of rate" would permit distinguishing the latter effect on germination from the former effect. The CBCC has maintained the single symbol meaning both "increase" and "accelerate", as well as the single symbol meaning both "decrease" and "slow", because the symbols were so defined in the early editions of the Code and, after a given date, the extensiveness of past use of each symbol with both meanings made impractical changing their definitions. For a new coding program, separate code symbols could be provided in Field T-1 for increase and accelerate, as well as for decrease and slow; the alternative to this would be to distinguish by separate definitions in Field T-2 quantitative change and change in rate when a single process may be affected by the test compound in either way. In the example given, this might be done by assigning Symbols 2611 and 2612 to those distinguishing terms, germination time and percentage germination.

7. Use of Symbols 1 and 2 when Field E is coded with a pathology and Field T-2 is coded with a symptom of that pathology and when the Field T-2 code symbol IDENTIFIES the state or process as being a pathological state or process

Many of the items of Field T-2 represent pathological states or pathological processes which test compounds may "produce" (Symbol 7 of Field T-1). Pathological situations are often complex, however, and frequently it is only a symptom (of a total disease coded in Field E) which is specifically treated or specifically responds to the test compound. In this case, the CBCC codes in Field T-2 a pathological state which represents the treated or responding symptom of the infectious or non-infectious disease coded in Field E.

Examination of the items of Field T-2 will reveal that many are defined so that the pathological aspect is clear. Examples of these are toxic symptoms (Symbol series 113-), abnormal morphologic changes (Symbol series 411-), histolysis (273), circulatory disturbances (Symbol series 87--), anemia (853), ventricular tachycardia (C122), etc.

Other items of Field T-2 are defined as normal biological qualities, states, or processes that can be affected (i.e., their definitions indicate no abnormality of these states or processes): e.g., number of fruits (191), nuclear shape (226), regeneration (272), aging (2C), venous pressure (8213), blood cell number (851), cardiac rate (C1), etc. Although none of these latter Field T-2 definitions include the word "normal", it is nevertheless implied.

If the pathological symptom treated with the test compound is one of those of the first type described above (Symbols 113-, 411-, etc.), the effect of the test compound is properly coded with Symbols 1 or 2 (or Symbol 3, if the condition is abolished or prevented).

However, if the symptom is a pathological variation of one of those normal states or processes described above as the second type of Field T-2 items (Symbols 191, 226, etc.), Symbols 1 and 2 must not be used, because they provide no indication that the test compound action coded in Field T-1 is not an increase or decrease from the normal level rather than from an abnormal level. Special Field T-1 items have been introduced which designate that the normal state or process in Field T-2 had been altered by pathology and that the test compound was administered to treat that altered Field T-2 state or process. These Field T-1 symbols are J, K, L, M, N, Ø, P, Q, and R. Symbol J, for example, is used for indicating that the normal state or process coded in Field T-2 had been diminished by the pathology coded in Field E and that the test compound had been administered to increase or speed the diminished state or process to bring it back to a normal level (i.e., cure the diseased organism). Symbol K is used for the situation reversed from that for which Symbol J is used and Symbol L is used when the normal state or process has been affected by the pathology and the test compound has been administered to restore the normal level by some action other than increase or decrease. Symbols J, K, and L, which code a cure of the diseased organism, are used instead of Symbol 3. Symbols M, N, and Ø are used to indicate improvement, but not a cure, of the organism and are analogous to Symbol 2. Symbols P, Q, and R code exacerbation of the disease and are used instead of Symbol 1.

In sorting the coded files for data on specific action of compounds, it is possible that one might want to retrieve data on all compounds that (e. g.) increased a state or physiological process, regardless of whether it was or was not increased from the normal level. If such were the case, it would be somewhat advantageous if, for all instances of increase of the state or process, Field T-1 were coded with Symbol 1, rather than having to sort out all that data for which Field T-1 was coded with Symbols J, M, and Q, as well as that data for which Field T-1 was coded with Symbols 1 and 2. However, in most cases, retrieval of data on all compounds that increase or speed a state or physiological process is preferably limited to those data in which the effect was an increase or acceleration from a normal level; i. e., it is preferred not to have included, with that retrieved data, information on compounds which merely corrected a state or process pathologically diminished or which exacerbated a state or process pathologically increased or accelerated. For this reason, it is useful to have the two types of data distinguished; thus, when retrieving information on increase or acceleration of a state, quality, or process from a normal level, omission of any data on increase or acceleration from a pathological level can be accomplished by eliminating any Field T-2 items identified as pathologies associated with the state, quality, or process concerned in the search and by elimination of any information coded with Symbol J, M, or Q in Field T-1.

In summary, when Field E is coded with a pathology and a symptom of the pathology is coded in Field T-2, Field T-1 is coded with Symbol 1 or P, Q, or R; 2 or M, N, or Ø; or 3 or J, K, or L, according to the character of the Field T-2 term. If the Field T-2 term is identifiable by its definition as a pathological state or process, Field T-1 is coded with Symbol 1 or 2 (or Symbol 3, if the pathological state or process is abolished--i. e., if a cure is effected). If the Field T-2 term representing a pathological symptom is identifiable only as a normal state or process, Field T-1 must be coded with Symbol J, K, L, M, N, Ø, P, Q, or R. This is discussed more thoroughly in Divisions 16 and 17 which explain in more detail the specific use of Symbols J through R.

8. Symbol 3; complete abolishment or prevention of a normal or pathological biological state or physiological process coded in Field T-2

When a test compound stops or prevents or is tested to stop or prevent a specific normal biological state or physiological process, Symbol 3 is used in Field T-1 and evaluation (Field Y) is based on the ability of the test compound to stop or prevent the normal state or process, rather than on the ability to cause some degree of decrease or slowing of the normal state or process.

However, when a test compound stops or prevents a specific pathological biological state or physiological process, the action is coded in Field T-1 with Symbol 3 only with certain Field T-2 entries; with other Field T-2 entries, Field T-1 must be coded with Symbol J, K, or L, as explained in the following paragraphs.

In Division 7, Field T-2 terms were described as being of two major types, one being of normal states or processes (e. g., number of flowers, Symbol 191; nuclear shape, Symbol 226; regeneration, Symbol 272), referred to in the first paragraph of the present discussion. The other type was described as consisting of pathological states or processes coded in Field T-2 (e. g., local toxicity, Symbol 113; atrophy, Symbol 411).

When a compound is administered to affect (rather than "cause", Symbol 7 of Field T-1) one of those pathological states or processes coded in Field T-2 as a term of the second type, that effect can be coded with Symbol 1 or 2, or if the pathological state or process is wholly abolished (cured) or prevented, the action can be coded with Symbol 3.

However, if a symptom (coded in Field T-2) of a pathology (coded in Field E) can be identified in Field T-2 only as a normal biological state or physiological process (i. e., if there is no indication in Field T-2 that the normal state or process has been rendered abnormal by the pathology in Field E) and the test compound is administered to affect that pathologically altered state or process, Symbol 3 can not be used if the compound returns the state or process to complete normalcy, because it would only be interpreted as having abolished or prevented the normal state or process.

As was pointed out in Division 7, when a pathology symptom is coded in Field T-2 only as the normal state or process which has been altered by the pathology, the special symbols J, K, and L must be used in Field T-1 instead of Symbol 3.

It will be noted that Symbol 3 is defined as the ultimate degree of the action coded by Symbol 2. Thus, in this case, two symbols are provided for the action of diminishing the state or process in Field T-2, one for any degree short of complete abolition or prevention (Symbol 2) and one for complete abolition or prevention (Symbol 3). This is basically the reason for having the two sets of symbols, (1), J, K, and L and (2) M, N, and Ø. If Symbols 3, J, K, and L were not included in Field T-1, all diminishing effects on states or processes in Field T-2 would necessarily have to be evaluated on the basis of the degree of diminution (Symbols 2, M, N, and Ø) and total abolishment could only be evaluated as a high degree of diminution.

9. Symbols 4 and 5; increase (or decrease), followed by the reverse action, decrease (or increase), on the biological state or process coded in Field T-2

The occurrence of this phenomenon as an action of test compounds and the use of Symbols 4 and 5 is relatively infrequent. When such a two-phased response is demonstrated, the CBCC coder always constructs a code line with Field T-1 coded with Symbol 4 or 5; if some circumstance makes apparently important the coding of an evaluation of only one phase of such a response (the increase or decrease phase), this must be done by a second code line with Field T-1 coded appropriately with Symbol 1 or 2 and a full explanation in the written abstract that this was only one phase of the response.

There is an evaluation problem (Fields X and Y) when the biological response to the test compound is characterized by reversing and when this reversal is indicated in Field T-1 by Symbol 4 or 5. When Symbol 4 or 5 is used in Field T-1, evaluation (Field Y) must never be made only on one phase of the response (i.e., on only the increase or only the decrease), but it must be made on the total response. This is possible with Criterion 62, if the percentage of individuals showing this characteristic reversal of response is determined (but not if the percentage measure is one of percentage of degree of increase and percentage of decrease); evaluation is possible also with the dosage criteria, 51, 52, and 53 (dose size vs. percentage of individuals showing the response with its characteristic reversal), or with Criterion 01. Evaluation might conceivably be possible with Criterion 13 or 54, if a time measure is the criterion and if evaluation is based on the total duration of response, both increase and decrease, but the CBCC has established a practice of never using Criterion 13 or 54 when Field T-1 is coded with Symbol 4 or 5; see Division 1 of the Specific Directions and Explanations for Field U. In other words, evaluation can not be made on the basis of any quantitative measure of only one of the phases of the response which involves two phases, if Field T-1 is coded with Symbol 4 or 5 to indicate the two-phased nature of the action.

10. Symbol 6; alteration of a biological state or activity (coded in Field T-2) whose alterations by a test compound are not appropriately expressed as an increase or decrease (Symbols 1, 2, 3, 4, or 5). Effects on physiological processes which disrupt the continuity or the periodicity of the process in a more complex way than simple increase, decrease, abolishment, or increase/decrease followed by reversal

A confusion in concept of the definition of Symbol 6 leads to occasional coding errors. This difficulty lies in misinterpreting the definition ("irregular", "fluctuating") to be a way of coding test results which indicate only that a physiological process was altered, but which do not indicate how it was altered (e.g., increased, decreased, stopped, made irregular). The CBCC has OMITTED coding data in which the action is not described except to say that some action (undefined) occurred altering the biological state or process coded in Field T-2.

When it is clear, however, that the action of the test compound has been to cause a physiological process to proceed irregularly (i.e., when it is clear that the altered physiological process does not follow its normal "regular" pattern, and the alteration is not a simple acceleration, simple slowing, abolishment, or a simple reversal), Symbol 6 should be used in Field T-1.

A number of Field T-2 items define normal biological balances. The disruption of a balance or of a normal proportion can not be expressed by the terms "increase" or "decrease". I.e., a balance or proportion can not be increased or decreased; only one of the balanced components can be increased or decreased to disrupt the balance. Therefore, when the entry in Field T-2 refers to a balance (nitrogen balance, Symbol F171; blood cell proportion, Symbol 852; and acid-base balance, Symbol 884), it is necessary to use Symbol 6 in Field T-1 to express the test compound's effect on it.

Similarly, the two Field T-2 items, general behavior of the individual or group (Symbols 55 and 56), can not be affected by test compounds in a way that can be described adequately as simply as "increased" or "decreased" or "stopped". Effects on behavior are complex and could only be coded by devising items for Field T-2 for those specific behaviors altered. Symbol 6 of Field T-1 is used with Field T-2 Symbols 55 and 56 merely to record that behavior has been made "irregular".

11. Symbol 7; induction or initiation of a biological state or physiological process coded in Field T-2; Symbol 7 is used when coding alteration, synthesis, or metabolic fate of the test compound or induction or initiation of alteration, synthesis, or metabolic fate of a secondary compound

Division 7 has pointed out that Field T-2 includes biological states, factors, or physiological processes of two general categories, the first being those that are normal (though they may be made abnormal), of which the following are examples: size of fruit, Symbol 191; hatching, Symbol 2E; appetite, Symbol F32; blood pressure, Symbol 821; fragility of blood cells, Symbol 874; clotting time, Symbol 8732; and breathing rate, Symbol B13. The second category includes those that specifically represent pathological states or processes, of which the following are examples: death, Symbol 11, 112, or 113; toxicity symptoms other than death, Symbol series 113- through 116-; morphological changes, Symbol series 41--; anemia, Symbol 853; edema, Symbol 872; hyperpnea, Symbol B17; and A-V block, Symbol C136.

With the former terms, which indicate normal states and processes, it is inappropriate to use Symbol 7, even if the process is discontinuous and the test compound influences it to occur at a time other than when it would normally occur (such as inducing "hatching" or "appetite" before they would normally occur). In other words, a test compound can be considered as increasing or decreasing appetite or speeding or retarding hatching, for example, but not as causing these normally occurring processes. (An exception might be the induction of a process which is normal in some organisms but happens to be unusual or does not occur in the particular test organism. For example, flowering might be induced in a plant species or variety which ordinarily seldom or never produces flowers but reproduces only vegetatively; the induction of flowering on such a plant by a test compound might reasonably be coded by Symbol 7 of Field T-1.) It is possibly more easy to discern the inappropriateness of using Symbol 7 with terms such as size of fruit, blood pressure, clotting time; these are not "caused" but are only "affected" (increased, decreased, or stopped) by test compounds. Even if these normal conditions and processes have been made abnormal by a pathology (i.e., if that normal condition or process coded in Field T-2 is understood to have been rendered abnormal and is a symptom of a more general disease, because Field E is coded with a pathology symbol), Symbol 7 would never be appropriate; in other words, if a normal process has been stopped as a result of the pathology coded in Field E, Symbol 7 should never be used to indicate that the test compound initiated the process again; this is done only by Symbol L or Ø of Field T-1.

It is with the second category of Field T-2 items (those whose definitions identify them as definite pathological states or processes) that Symbol 7 is properly used, but only when Field E is not coded with a pathology. Even under the condition of the test organism being in another, pre-existing pathological state, and even if the test compound had been administered with the intent to treat the pre-existing pathology, the pre-existing state would not be coded in Field E in the code line recording the test compound's action in producing (Symbol 7) a second pathology. Instead, the test organism would be coded in Field E and Field G would record the organism's being in an unspecified pathological state. Thus, if Field E is coded with a pathology of a host in Field J, any pathological aspect coded in Field T-2 must have been caused by that pathology in Field E; it can only be corrected or exacerbated by the test compound, the correction or exacerbation being indicated by Symbol 1, 2, or 3 in Field T-1, never by Symbol 7. Therefore, in general (see exceptions described below), Symbol 7 is used only to code the test compound's causing a pathological state which can be coded in Field T-2 with a symbol whose definition is explicitly of a pathological nature (i.e., a Field T-2 item of the second category described above); the pathological state will be coded as having been caused in a test organism coded in Field E.

Exceptions to the restrictions in use of Symbol 7 as just described (for causing a pathological state or process defined precisely as pathology by the symbol in Field T-2 and with Field E coded with the test organism) are described below, involving Field T-2 symbols of the following series: 16--, 17--, FE--, FF--, F6--, F8--, F9--, FA--, FB--, FC--, FG--, FH--, and FI--.

Symbols of the 16-- and 17-- series of Field T-2 are used when a pathology is coded in Field E, but they are somewhat unique in that they do not represent a pathological state (i. e., they do not represent a symptom of the pathology coded in Field E). Instead, they represent a state (e. g., "cure", "restraint", or "intensification") or symptom (e. g., "reduction [or increase] of the number of pathogen individuals") of recovery from or of exacerbation of the general pathology coded in Field E. With any of these symbols in Field T-2, Symbol 7 is used in Field T-1, even though Field E is coded with a pathology, to code the test compound's "bringing about" that state of recovery or exacerbation.

Symbol 7 is used to describe what is essentially an action of the biological system on the test compound (rather than an action of the test compound on the biological system), a use which is described in Division 2. This represents an exception to the general rule that Symbol 7 is never used when Field T-2 is coded with a symbol defined as a normal physiological process. These Field T-2 items deal with the alteration of the test compound or a secondary compound by the biological system (Symbol series FE--) or with the synthesis or metabolic fate of the test compound or secondary compound (Symbol series F6--, F8--, F9--, FA--, FB--, FC--, FF--, FG--, FH--, and FI--).

When the test compound has been altered, synthesized, or metabolized, Field T-2 is coded with the appropriate term (FE--, FAB, FBB, FGB, FIB, or FF-B) and Symbol 7 is used in Field T-1 to mean that the test compound "is oxidized", or "is excreted" or "is stored", etc. (i. e., "undergoes oxidation" or "undergoes excretion" or "undergoes storage", etc.) by the normal organism coded in Field E.

When the test compound affects the alteration, synthesis, or metabolism of a secondary compound, Field T-2 is coded with the appropriate term (FE-- with an asterisk in Column 61, F6-, F9-, FA-, FB-, FG-, FH-, FI-, or FF--) and Field T-1 is ordinarily coded with Symbol 1, 2, or 3, since the affect is generally one of increase, decrease, or arrest. However, it is possible that the test compound may initiate or permit the alteration, synthesis, or metabolism of the secondary compound and for this Symbol 7 would be used.

12. Symbols 8, 9, and C; coding of the test compound's influence (Field T-1) on the action (not coded) of another compound (Field D) on a biological state or physiological process (Field T-2); depression ("antagonism") or enhancement (either "synergism" or simple "additive effect"); Symbols 9, 8, and C, respectively

Five general aspects of experimental data demonstrating synergism, antagonism, or additive effect (Symbols 9, 8, and C) are dealt with in this division. (A related aspect, which might be considered a sixth, is that concerned with coding of a test compound's being essential for or permitting the action of a secondary compound, coded by Symbol 8; to avoid making further complex the distinctions made here in Division 12, this matter is discussed separately as Division 13.) These five are:

(1) Definitions, according to which the test compound's effect can be distinguished as one or the other of antagonism, synergism, or additive effect.

(2) Determination of which compound, of the two compounds involved in such investigations, should be coded as the test compound and which should be coded as the secondary compound.

(3) The use of Field T-1 to code these effects on the action of a second compound, a use which prevents coding that action affected. This problem includes the aspects of preparing code lines for recording the action antagonized, synergized, or supplemented, as well as the action of the antagonist, synergist, or additive agent when administered alone.

(4) Coding when a compound is tested to affect (synergize, antagonize, or be additive in affecting) the synergistic or antagonistic effect of a secondary compound on a third compound's action on the biological state or physiological process coded in Field T-2. This coding procedure is dependent on factors and procedures related to the third aspect above.

(5) The criteria (Field X) by which each of these three influences of test compounds (on actions of secondary compounds) can be evaluated (Field Y).

Of these five, definitions are discussed first. In this general discussion of definitions and in the specific definitions, the second of the aspects listed above is essentially ignored so that, in the paragraphs immediately following, any reference to the test compound and the secondary compound should be accepted as implying that the choice of compounds as the test compound and secondary compound has been made appropriately. The final part of this division discusses the second, third, and fourth of the aspects listed above. The criteria for evaluation (the fifth aspect) are indicated immediately following the discussion of each of the definitions.

Concepts of meaning of any of the terms, "antagonism", "synergism", and "additive effect" are not always constant; for example, a given measure of depressant effect of a test compound on the action of a secondary compound may represent antagonism according to one author's concept, but not to another's concept. To establish consistency in coding, these terms have each been given a precise definition for CBCC use to which definitions the coder must match the data presented by the author to determine if those data demonstrate synergism (Symbol 8), antagonism (Symbol 9), or additive effect (Symbol C), according to those CBCC definitions. These three test compound effects or influences on the actions of secondary compounds are distinguished on the basis of measurement of intensity of response of the test organism to the secondary compound administered alone and the measurement of intensity of response of the test organism to the test compound administered alone and the comparison of the calculated sum of these two intensity measurements to the measurement of actual intensity of response when the two compounds are administered together (i. e., administered so that they are exerting their effects [on the test organism and each other] simultaneously). Use of the expression "administered together" in this division does not imply that the physical act of administration of the two compounds need be simultaneous, such as simultaneous injection or administration as a mixture.

In organizing these definitions of effects or influences of the test compound, they have been grouped under two headings, (A) enhancement of that intensity of the organism's response to the secondary compound (i. e., enhancement of the intensity of response to the secondary compound administered alone) and (B) depression of that intensity of the organism's response to the secondary compound administered alone. Four graphic representations are included, as Figures 1 through 4, to assist in understanding these definitions.

A. The test compound enhances the intensity of the organism's response to the secondary compound, as determined by comparison to the intensity of response when the secondary compound is administered alone: (1) synergism or (2) additive effect. These are distinguished below specifically by statements (1) and (2), qualified by conditions expressed as I and II.

I. Action of the test compound and of the secondary compound, when administered alone, are KNOWN to be the same (i. e., their actions are known not to be opposing) and intensity of action of the test compound when administered alone is KNOWN. (See Figure 1.)

(1) Synergism (See Figure 1.): The intensity of action, when the compounds are administered together, is greater than the sum of the intensities of action of the two compounds when each was administered separately and in the same dose quantity as when administered with the other. For this, use Symbol 8. Example: Compound B, when administered alone at 100 mg/kg, caused 40% increase in a normal physiological process (e.g., blood pressure); Compound C, when administered alone at 50 mg/kg, caused 10% increase in the same physiological process; when administered together (100 mg/kg of Compound B and 50 mg/kg of Compound C), the response intensity was 80% increase in that physiological process. This being 30% greater than the sum of the intensities of the action of the two compounds when administered alone, the test compound's influence is interpreted as synergism. (To be a synergist, a test compound need not cause the response to any degree when administered alone, though it may as suggested by the definition above and the figure.)

Evaluation of Synergism: For this effect or influence of the test compound on the action of the secondary compound, no special criterion is included in Field X. It is coded only by Criterion 61 or 62 by which is expressed the per cent increase of intensity of action, over the sum of the intensities of action of the two compounds when administered alone. (Earlier efforts to establish a criterion for synergism [correlating with the synergistic increase in intensity of response the

relative quantities of the test compound and secondary compound involved] have been felt insufficiently developed and too complex to include in the present edition of the Code.)

(2) Additive effect (See Figure 1.): The intensity of action, when the compounds are administered together, is equal to or not significantly different from the sum of the intensities of action of the two compounds when each was administered separately and in the same dose quantity as when administered with the other. For this, use Symbol C. Example: Consider the example used above to illustrate synergism: If the intensity of response when the two compounds were administered together were 50%, or not significantly greater than or less than 50%, the test compound's influence is interpreted as an additive effect. Note the following special situation and the provision for it: If the intensity of response when the two compounds are administered together is not as great as the sum of the response intensities when each is administered alone, yet is more than the intensity of response of the compound coded as the secondary compound when administered alone, the CBCC uses Symbol C. In the example used above to illustrate synergism: If the intensity of response when the two compounds administered together were of any degree more than 40% and less than 50%, the CBCC would code in Field T-1 the effect or influence of the test compound on the action of the secondary compound as being "additive with the secondary compound", using Symbol C. However, if the intensity of response when the two compounds are administered together is not only less than the sum of the response intensities of each when each is administered alone, but is less than the intensity of response of the compound coded as the secondary compound when administered alone, the CBCC interprets the test compound effect as antagonism (Symbol 9), described below (B, I, [2]).

II. Actions of the test compound and secondary compound when administered alone are NOT KNOWN to be the same (are not known to be the same or opposing) and/or intensity of action of the test compound when administered alone is NOT KNOWN. (See Figures 2 and 4.)

If the intensity of action of the secondary compound when administered alone is known, and the action of the test compound is known to be the same as the action of the secondary compound (Figure 2) or to be the opposing action (Figure 4), but the intensity of action of the test compound is unknown (both Figures 2 and 4), it can not be determined, when the intensity of response to the secondary compound is enhanced, if the influence of the test compound is synergistic or merely additive. In such cases (when the intensity of response to the secondary compound is enhanced), the CBCC has established the convention of coding Field T-1 with Symbol C; i.e., treating the data as additive. Under these circumstances, the written abstract should make clear in Field T-1 that the test compound's being additive or synergistic has not been determined: If only one word is written in Field T-1, it should be "increase", rather than "additive", even though Symbol C is entered in the code box.

Evaluation of additive effect: When a code line is constructed for recording specifically the fact that the two compounds administered together produce a response that is additive (i.e., one compound does not synergize or antagonize the action of the other), there is a peculiar problem of evaluation in Field Y, since the quality of "additiveness" can scarcely be described in degree. Only Criterion 01 can be used in Field X when Field T-1 is coded with Symbol C. However, because of the special provision, described in I (2) above, for using Symbol C under circumstances when the intensity of response to both compounds administered together is to a limited degree less than precisely additive, Field Y is coded in the following various ways: When the results are exactly additive (i.e., an actual additive effect; for example, 50% in the illustration of A, I, [2]), it is indicated in Field Y by using Symbol 9 (Symbol C in Field T-1). On the other hand, if the response when the two compounds are administered together is only slightly more than the response of the most active of the compounds when

administered alone (only slightly more than 40%, in the foregoing illustration), Field Y is coded with Symbol 3. Otherwise (42% through 49%, in the foregoing example), Field Y is coded with Symbol 0. Finally, in the event that response intensity should be only exactly equal to that of the most active of the compounds when administered alone (exactly 40%, in the foregoing illustration), Field T-1 should be coded with either Symbol C or Symbol 9 and Field Y should be coded with Symbol 1 (with Criterion 01 coded in Field X) to indicate that the additive or antagonistic effect did not occur. Field T-1 need not be double coded nor two lines prepared in this case, because by coding the fact that one (C or 9) occurred, it is implicit that the other (9 or C) did not occur.

B. The test compound depresses the intensity of the organism's response to the secondary compound, as compared to the intensity of response when the secondary compound is administered alone.

I. Specific action and intensity of action of each compound (of the two compounds involved), when it is administered alone, is KNOWN. (See Figures 1 and 3.)

If the intensity of action of the secondary compound when administered alone is known and the intensity of action of the test compound when administered alone is also known, it can be determined (when the two are administered together, each in the same quantity as when it was administered alone) whether the test compound's influence is one of antagonism to the secondary compound's action (Symbol 9). Antagonism of a secondary compound's action may be by a test compound which, when administered alone, performs the same action (though not to the same degree) as the secondary compound (e. g., both increase or both decrease the biological state or physiological process coded in Field T-2) or the antagonism may be by a test compound which, when administered alone, performs the opposing action (one compound increases and the other decreases the biological state or physiological process coded in Field T-2, when administered alone). Antagonism is described below (1 and 2) for each of these situations.

(1) Antagonism, when the test compound and secondary compound produce opposing responses when administered alone. (See Figure 3.) If, when administered together, the response is the same as when the secondary compound was administered alone, but at a lower intensity, the effect of the test compound is coded as antagonism; also, if no response occurs when the two are administered together or even if a response occurs opposite to that made to the secondary compound when administered alone, the effect of the test compound is coded as antagonism.

Note: In reference to the last-mentioned circumstance (when the response to the two compounds administered together opposes the response to the secondary compound when administered alone), the results should be coded as antagonism of the secondary compound as long as the intensity of that opposing response is equal to or less than the intensity of response to the test compound when administered alone. However, when the intensity of that response opposing the secondary compound's is greater than the intensity of response to the test compound when the test compound is administered alone, a second code sheet should always be prepared on which a code line is constructed whereby the secondary compound of the first line is coded as the test compound synergizing the action of the compound coded in the first line as the test compound. This is indicated by Figure 3.

(2) Antagonism, when the test compound and secondary compound cause the same response but in different intensities when administered alone or when the test compound did not affect the biological state or physiological process of Field T-2 when administered alone. (See Figure 1.) If the intensity of response, when the compounds are administered together, is less than the intensity of response to the secondary compound when administered alone, the effect of the test compound is coded as antagonism.

Evaluation of antagonism: For this, Criteria 22 and 55 may be used, if the intensity of response has been reduced to zero (in case the test compound did not produce the response when administered alone) or if the intensity of response when the compounds are administered together is not greater than the intensity of response when the test compound was administered alone (if the test compound did produce the response when administered alone). Either of these intensities of antagonism represents 100% antagonism of the secondary compound's action for which Criteria 22 and 55 are defined. If the intensity of response to the two compounds administered together is more than the intensities just described (0 or more, but no greater than the intensity of response to the test compound when administered alone), Criterion 62 must be used.

II. Intensity of action of the test compound, when administered alone, is NOT KNOWN and the action of the test compound is NOT KNOWN to be the same as or to be opposite to the action of the secondary compound. (See Figure 4.)

This situation is discussed above under heading A (A, II). If the intensity of response, when the two compounds are administered together, is greater than the intensity when the test compound is administered alone, the CBCC codes the compound's effect as being additive, Symbol C. If the intensity of response is less than the intensity when the secondary compound is administered alone, the CBCC codes the test compound's effect as being antagonism of the secondary compound, even if the action is opposite to that of the secondary compound when administered alone. Evaluation of the additive effect or of the antagonism is according to the explanation made above, following A, II and following B, I, (2).

The four figures on the following page are included to assist the coder in understanding the foregoing explanations of antagonism, synergism and additive effect.

The second aspect of coding synergism, antagonism, and additive effect, listed at the beginning of this division, is that of determining which, of two compounds administered together, shall be coded as the acting agent (test compound, synergist, antagonist, or additive agent) and which shall be coded as the affected compound (secondary compound, synergized or antagonized compound, or compound whose effectiveness is merely supplemented, any of which would be coded in Field D) or, particularly in the case of synergism and additive effects, whether each of the two compounds should be considered in turn as the synergist or additive agent.

In most cases of antagonism (Symbol 9), the choice is not the coder's responsibility and has been stipulated by the author. Ordinarily, a compound candidate for antagonism of another compound is one that, when administered alone, causes no response or causes the response at a considerably lower intensity than do the compounds it is expected to antagonize. In any case, only one of the two compounds is to be regarded as the antagonist and only one line is to be coded.

When synergism (Symbol 8) has been demonstrated, it is frequently impossible to ascribe the increased intensity of action of the two compounds administered together to one or the other of the two, even if one of the compounds were inactive when administered alone; i. e., it is frequently impossible to discern which compound was synergized and which acted as a synergist.

In the case of an additive effect (Symbol C), there is no real discrimination between the two compounds as being either the compound whose action was added or the compound whose action was added to.

Nevertheless, the CBCC does not prepare a code line (on a second Code Sheet) for the secondary compound in which that compound would be coded as the test compound synergizing or adding to the action of the compound coded on the first Sheet as the test compound. The CBCC restricts this coding to a single line by selecting only one of the compounds to be coded as synergist (or as a compound showing additive effect). With respect to this selection, if a whole series of chemicals are tested for their synergistic or additive effect with one chemical, the chemicals in the series should be regarded and coded as the test compounds and the single chemical against which they are tested should be regarded and coded as the secondary compound. Therefore, if the CBCC files are searched for (1) all activities of given compounds or for (2) all compounds showing synergism or

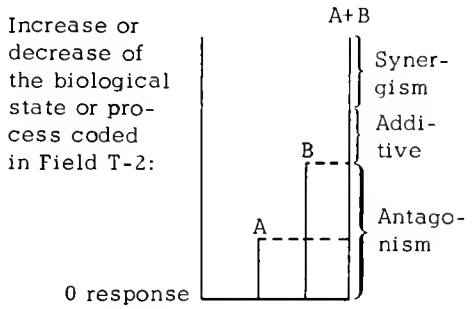


Figure 1

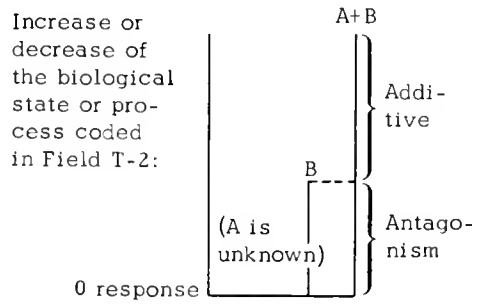


Figure 2

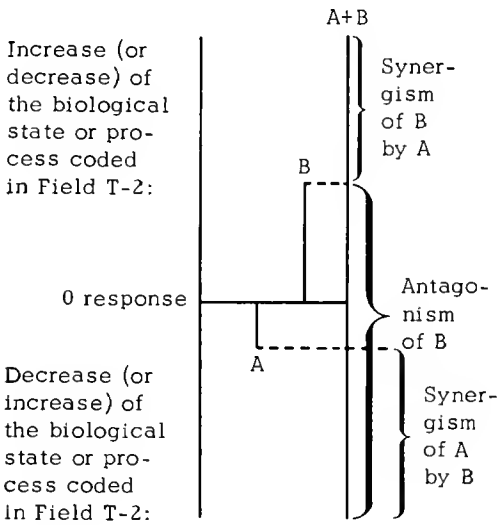


Figure 3

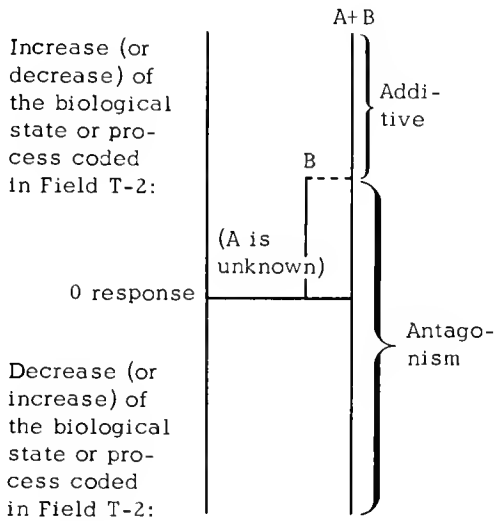


Figure 4

Key to the figures:

A --- Intensity of response induced by the test compound when administered alone.
B --- Intensity of response induced by the secondary compound when administered alone.
A+B --- Intensity of response induced by the test compound and secondary compound when administered together.

Figures 1 and 2: The test compound and secondary compound cause the same response when administered alone (though at different intensities).

Figures 3 and 4: The test compound causes a response opposite to that caused by the secondary compound (Fig. 3) or the test compound's causing the same or the opposing response to the secondary compound is not known (Fig. 4).

Figures 1 and 3: The intensity of response to the test compound when administered alone is known.

Figures 2 and 4: The intensity of response to the test compound when administered alone is unknown.

additive effects on a given test compound, it is necessary (and adequate) to sort for IBM punched cards (and Code Sheets) with those compounds coded in Field D and with Symbols 8 or C in Field T-1; these will represent synergists or additive agents as well as the compounds coded as test compounds on those code sheets and IBM punched cards. For example, if there were wanted all compounds which have been tested as synergists or additive agents for Compound "X", all cards would be pulled for the Compound "X" from the serial file and a sort made for Symbol 8 or C in Field T-1; however, the compound may have been coded as the secondary compound in synergist or additive action tests and therefore the secondary compound file should also be checked for Compound "X" and a sort made in Field T-1 for cards coded with Symbols 8 or C. Similarly, if there were wanted all compounds tested as antagonists of Compound "X", it is probable that, to be thorough in the search, the secondary compound file should be sorted for Compound "X" as well as the serial file, followed by a sort in Field T-1 for Symbol 9.

The third aspect listed at the beginning of the division is that of the inability to code the action of the secondary compound (i. e., the action on the biological state or process coded in Field T-2) which has been antagonized, synergized, or supplemented; this is because Field T-1 is used to code the antagonism, synergism, or additive effect. In support of the omission, it is pointed out that, in many instances, the secondary compound antagonized, synergized, or supplemented and its action on the biological state or physiological process coded in Field T-2 are so widely known (by persons coding data and subsequently correlating the coded data) that the code entries in Field D (the compound's identity) and Field T-2 (the biological state or physiological process affected by the secondary compound) are fully adequate to indicate the uncoded action of the secondary compound affected by the test compound. While this is a justifiable concept, and would be especially so in coding projects of limited scope, the wide and varied area which the CBCC attempts to cover does not permit ignoring coding the specific action of the secondary compound in all cases. Therefore, for CBCC coding, some attention must be paid to coding the action of the secondary compound affected by the test compound. Neither does the line in which is coded a test compound's antagonistic, synergistic, or additive effect permit a code indication of the test compound's action when administered alone. This also must be given some consideration.

When coding antagonism, synergism, or additive effect, a second Code Sheet is never prepared by the coder to code the action (Field T-1) of the secondary compound, unless instructed to do so. However, the coder should always ascertain that a line is constructed for the test compound (antagonist, synergist, or additive agent) to accompany the line coded with Symbol 8, 9, or C (on the same code sheet), to code the test compound's action, when the data are given from a test demonstrating that action, on the biological state or process coded in Field T-2. This is because the compound tested as an antagonist, synergist, or additive agent is less apt to be a compound whose action is already recorded in the CBCC files and without such a code line, it would not be possible to retrieve data from the file basing a sort on that test compound's action on the biological state or process. The following example illustrates coding as just described. The example concerns an additive effect but it also illustrates the basic pattern for synergism and antagonism:

> Compound A and Compound B have an additive effect in reducing heart rate. Compound A reduced heart rate 5% when administered alone at 200 mg/kg and Compound B reduced it 10% when administered alone at 50 mg/kg. When Compounds A and B are administered together, each at the same dose level as when administered alone, the heart rate is reduced 15%.

Selecting Compound A as the test compound:

	D	N	T-1	T-2	X	Y
Line 01:	Cpd. B	67	C	C1	01	9
Line 02:	---------	67	2	C1	62	0

(A line for these data might be constructed at the Center [not by the coder] for Compound B, on a second Code Sheet, identical to line 02 above [except for the Field N entry, which would be 66]; however, for the latter compound on the second Sheet, no "additive" code line would be prepared.)

Although the situation outlined as the fourth aspect at the beginning of this division occurs infrequently, it is not unknown; the CBCC has had to establish a coding precedent for it at least to indicate that two compounds were demonstrated to be additive in antagonizing the action of a third compound.

The following example illustrates the coding for the data of the type just described.

Indole and skatole have an additive effect in inhibiting contraction caused by acetylcholine. (No other information is given.) Selecting one (indole) of the two compounds (indole and skatole) as the test compound, the coding is as follows:

D	T-1	T-2	X	Y
Skatole	C	813	01	0

In the language portion of Fields T-1 and T-2 of the line above, write, "Additive with skatole in antagonizing muscle contraction caused by acetylcholine; see the line below."

A second line for that compound selected as the test compound (indole) would be constructed on the same Code Sheet, in the following pattern:

D	T-1	T-2	X	Y
Acetylcholine	9	813	01	0

In the language portion of Field T-2 of the second line above, the following should be written: "Muscle contraction caused by acetylcholine; when administered with skatole, this activity for the two compounds is additive; see the line above."

(In addition to the two lines coded above for these data, a second Code Sheet is prepared especially for skatole to code a line identical to line 02 above. A second line on this second Sheet for the "additive effect" with indole will not be coded. The CBCC probably would find unnecessary preparing a third Code Sheet to code acetylcholine's action, "causes" [Symbol 7], on muscle contraction.)

Occasionally, evaluation of a synergistic or antagonistic action is made on the basis of comparison with a standard compound (Criterion 03 or 04 of Field X), resulting in competition for the use of Field D to code the antagonized or synergized compound as well as the standard compound to which comparison is made. This is resolved by coding two lines, both with Symbol 8 or 9 coded in Field T-1 but with Field D coded differently; in one line, Field D is coded with the compound synergized or antagonized and evaluation is based on Criterion 01 only; in the second line, Field D is coded with the standard compound, Symbol * (the IBM 12 zone punch) is coded in Column 17 of Field D, and Field X is coded with Criterion 03 or 04. (See the specific directions and explanations for Field D, Division 11, Conflict B.)

13. Coding of the test compound's being essential for (permitting or initiating) the action of the secondary compound

The situation in which a compound shows no biological activity until it is administered with another compound is closely related to the situation in which the first compound does show biological activity when administered alone but is synergized by the compound administered with it to produce a much greater intensity of biological response. The CBCC uses Symbol 8 to code both situations.

When a test compound has been demonstrated to be essential for (permit or initate) the alteration, synthesis, or metabolism of a secondary compound, Symbol 7 is used as explained in Division 11.

14. Symbol A; coding of the test compound's simulation of, or substitution for (replacement of), a second compound coded in Field D

Two compounds may affect a biological state or physiological process in a nearly identical fashion, even though their potencies for producing this effect may differ; in this respect, each can be considered as simulating the other. Ultimately, using this basic concept, all compounds shown to affect a given biological state or physiological process (e.g., heart rate or smooth muscle contraction) in the same way (e.g., all compounds that increase heart rate or all compounds that cause smooth muscle contraction) might be said to simulate each other with respect to this biological response. Most frequently, however, it is a relatively unknown or untried chemical that is described

as simulating, by its action, a chemical whose action is already familiar to the author or is widely known. Many compounds will come to mind whose actions have been so long observed and so thoroughly measured that their actions are virtually classic standards. Examples of these are the best known effects of digitalis, adrenaline, acetylcholine, curare, etc. However, compounds that are less familiar than the examples named may be demonstrated by test data as being simulated by the test compound.

Besides considering "simulation" as restricted to comparison to chemicals whose simulated action has previously been investigated and understood, it should be noted that generally an author implies by the term "simulation" that the two compounds act through the same mechanism (i. e., act through the same anatomical, physiological, or biochemical paths) to bring about the specific response such as reduction of heart rate, lowering of perspiration rate, increase of blood pressure, etc.

Neither of these restrictions to the use of the term "simulation" for description of chemicals' actions is absolute, but they are mentioned here to help explain that merely because two compounds cause the same response, they are not always (or even frequently) specially described by an author as simulating each other except when, by doing so, it assists significantly in describing a test compound's action.

Symbol A has been provided to code the fact that the test compound's action on the biological state or physiological process coded in Field T-2 is essentially similar to the action of another compound, to be coded in Field D. Simulation, as well as replacement, is ordinarily (although not necessarily always) expressed by an author only under the restrictive conditions mentioned in the first paragraphs of this division. Therefore, Symbol A is used only when an author states that the test compound has been demonstrated to simulate or substitute for a specific secondary compound. Simulation is sometimes expressed by the author with one of certain terms referring to a specific chemical and implying all aspects characteristic of its action, such as "nicotinic", "muscarinic", or "atropinic". For such data, nicotine, muscarine, or atropine would be coded in Field D and Symbol A would be coded in Field T-1, assuming that the nicotinic, muscarinic, or atropinic effect was on a specific biological state or physiological process coded in Field T-2. In case the author uses such terms to describe a test compound's general effects on an organism without specifying a biological state or process affected, this general simulation is not coded with Symbol A, but the general effect is coded in Field T-3, if the appropriate term is available in Field T-3 (nicotinic effect, atropinic, etc.), Field T-2 is coded with Symbol 14 which refers to Field T-3, Field T-1 is coded with Symbol 7 instead of Symbol A, and it is unnecessary to code in Field D the compound simulated.

When the compound simulated is a normal constituent of the organism or an essential dietary component and the simulation is the test compound's ability to substitute adequately for that normally occurring compound, the test compound is more frequently described as functionally "replacing" that secondary compound than as simulating it.

Each time the evaluation of a test compound's action is expressed in terms of comparison to a standard (Criteria 03 or 04 of Field X), the situation involves two compounds that simulate each other, even if their potencies for the action they both perform are not the same.

Although Criteria 03 and 04 (Field X) necessarily involve two compounds simulating each other, they can not be used for evaluating that simulation or replacement (i. e., when Field T-1 is coded with Symbol A); in the reverse, when evaluation of a test compound's action is made on the basis of Criterion 03 or 04, Symbol A should not be substituted in Field T-1 for the action being so evaluated.

Note that by using Field T-1 to denote that a test compound's action simulates or replaces, there is omitted any specification of the actual action performed and simulated. Therefore, a problem exists similar to the problem of not being able to code the action when Field T-1 is coded with Symbol 8, 9, or C, discussed in Division 12.

When Symbol A is used to indicate that the test compound replaces a normal constituent or dietary component, the role that constituent or dietary component normally plays in the organism need not be recorded and therefore a second line especially to code this is not constructed. However, when Symbol A is used to indicate that the test compound action simulates the action of a secondary compound which is not a normal constituent or dietary component, the action simulated is not to be construed by the CBCC coder as always obvious to every potential user of the coded information. When

the data include description of the action as well as the stipulation that the action simulates that of a second compound (instead of indicating only the fact that the test compound simulated the second), a line should be constructed to code this action of the test compound on the same Code Sheet.

15. Symbols D, E, F, and G; coding of the test compound's influence (Field T-1) on the action (not coded) of a nerve (Field H) on a physiological process (Field T-2)

In the same way that a test compound may alter the action of a secondary compound (see Division 12, Symbols 8 and 9), a test compound can influence the action that a specific nerve has on a given biological part or process. Examples of such processes controlled or affected by nerves are heart rate (Field T-2, Symbol C1), vascular dilation (Symbol 8215), gland secretion (Symbol FC), skeletal muscle contraction (Symbol 813), etc. When a test compound intercedes in this nervous control or nerve effect, it should be coded specifically as such. The situation exists particularly in the case of those tests using anatomical preparations (frequently in vitro) which consist of an effector end organ (heart, skeletal muscle, gland, etc.) and its controlling anatomical nerve. The normal nervous effect on the end organ is demonstrated and measured by artificial stimulation of the nerve; subsequently, the test compound is administered, its effect being interpreted as the alteration of the degree of the end organ's response to the nerve, when the nerve is given a stimulus equal to that stimulus administered prior to administration of the chemical. For such special data, four symbols are provided, D, E, F, and G.

Symbols D and E are used to indicate that the test compound acts to inhibit the nerve's normal action; Symbols F and G are used to indicate that the test compound acts to intensify the nerve's normal action. It will be recalled that, in the case of coding a test compound's effects on a secondary compound's action (e.g., Symbols 8 and 9 of Field T-1), the secondary compound's action can not be coded; similarly, when coding a test compound's effect on the action of a nerve, there is no special coding field in which to code the nerve's normal action. This disadvantage, however, is largely compensated for by having two symbols for each of inhibitory and intensifying chemical action, one symbol (D or F) indicating that the nerve normally increased or caused the biological process coded in Field T-2, the other symbol (E or G) indicating that the nerve normally inhibited or prevented the biological process.

Use of these symbols and coding of chemical effects on nerve actions on end organs is discussed in Division 8 of Specific Directions and Explanations for Fields H-1 and H-2.

16. Symbols J, K, L, M, N, and Ø; coding of the test compound's ameliorative or curative action on a pathological state or process, coded in Field T-2 as a symptom of a disease coded in Field E; return of the test organism to a normal state

The coding of pathology is dealt with extensively in the Key section on the Pathology Code of Field E, as well as in certain previous divisions of these specific directions and explanations for Field T-1 (Divisions 7, 8, and 11). In the section of the Pathology Code, it is explained that the CBCC takes advantage of Field T-2 to code specific symptoms of general pathological states coded in Field E, when the response of those specific symptoms represents the test compound's effect rather than the response of the entire symptomatology of the disease.

As has been pointed out in previous divisions (especially Divisions 7, 8, and 11), the items of Field T-2 are of three categories. Of these, the two major types (distinguished in Divisions 7 and 8) are:

(1) Those representing normal states or processes that can be affected by test compounds or by pathologies coded in Field E.

(2) Those that represent pathological states or processes that can be caused by the test compound or treated by the test compound.

The third category (described in Division 11) consists of Field T-2 terms representing stages of cure or partial recovery from a disease coded in Field E (Field T-2 items of the 17-- series) or stages of exacerbation of a disease coded in Field E (Field T-2 items of the 16-- series), all of which are coded only with Symbol 7 of Field T-1.

The coding of the test compound's producing a pathological state is discussed in Divisions 7 and 11: In coding the test compound's production of a pathological state or process (Symbol 7 of Field T-1), only those items of Field T-2 may be used which are of the second category described above.

When a pre-existing pathological state (coded in Fields E and T-2) is treated with the test compound, Field T-1 must be coded distinctively to indicate that the compound did not cause the pathology. The following paragraphs describe this specific coding.

If the entire disease, as is coded in Field E, responds to the treatment, Field T-2 is coded with the appropriate symbol of the 17-- and 16-- series (the third of the categories of Field T-2 items) and Field T-1 is coded with Symbol 7.

However, if only the pathological symptom of the general disease coded in Field E responds to the treatment (this symptom being coded in Field T-2 as one of either the first or second categories of Field T-2 items), Field T-1 must be coded to indicate the effect on that particular pathological state in returning it to normal (curing it or stopping totally progress of a morphological change, even though morphologic normality is not restored), returning it toward normal (improving the organism's condition or restraining the progress of the pathology, but not curing it or not stopping totally progress of a morphological change), or worsening the condition (exacerbating the pathological state). The coding of Field T-1 to indicate a test compound's effect on a pathological symptom coded in Field T-2 depends on the category of the Field T-2 terms to which the symptom belongs, as follows.

If the pathology symptom is one of the second category of Field T-2 items (i. e., an item specifying pathology, such as apnea, anemia, etc.) and if only the symptom coded in Field T-2 responded to the test compound, the test compound's effect is coded by Symbols 1, 2, or 3. Partial reduction or arrest of progress but not a cure of the pathology symptom is coded by Symbol 2 of Field T-1 (reduction of dyspnea, pain, anemia, or atrophy, e. g.); cure, total reduction, or prevention of the pathology symptom coded in Field T-2 or restoration of a pathologically totally suspended physiological process, is coded by Symbol 3 of Field T-1 (cure of or prevention of abscess, inflammation, or ventricular fibrillation, e. g.; complete stoppage of necrosis; restoration of normal function from states of sinus arrest or respiratory arrest, e. g.); and exacerbation of the symptom is coded by Symbol 1 (increase of irritation, degeneration, edema, e. g.). Note that if a test compound causes (Symbol 7 of Field T-1) a pathological state indicated by one of these Field T-2 items of this second category when it is administered to treat another pre-existing pathology, the pathology produced by the compound is not to be coded as a symptom of a disease coded in Field E; instead, the host of the general pathology is coded in Field E as the test organism and Field G is coded to indicate the fact that the organism is in an unspecified pathological state in which the test compound causes the pathological condition to be coded in Field T-2.

If the pathology symptom is one of the first category of Field T-2 items (i. e., an item describing a normal biological condition or process) and if only the symptom coded in Field T-2 responds to the test compound, the test compound's effect must be coded by one of a group of symbols provided in Field T-1 especially for this purpose. These are the nine symbols indicated on the IBM punched card by the 11 zone punch (Symbols J through R), J, K, and L being for curative effects, M, N, and Ø for effects in improving but not curing the symptoms, and P, Q, and R for effects in exacerbating the symptom. Symbols P, Q, and R (exacerbation) are discussed in the next division.

Of the first of these groups, Symbol J is used to indicate that the test compound increases the biological process which is in a pathological state, and in increasing it, returns it to its normal state, indicating that the process coded in Field T-2 had been in a pathologically depressed state when treated. Symbol J would also be used to code the test compound's restoration of a pathologically totally suspended physiological process. In the reverse, Symbol K is used to indicate that the test compound decreases the biological process which is in a pathological state, and, in decreasing it, returns it to its normal state, indicating that the process coded in Field T-2 has been at a pathologically elevated level or accelerated pace. Symbol K would be used also to indicate that the test compound stopped a pathological process initiated by (instead of increased by) a general pathology coded in Field E. Symbol L is used to indicate that the test compound acts in some way other than to increase (or restore) or decrease (or halt) a depressed (or abolished) or accelerated (or initiated) process to return it to the normal state; for example, Symbol L would be used to indicate returning to normal a physiological balance which had been pathologically altered (nitrogen balance, e. g.) or restoring to normal the general behavior of the organism (Symbol 55, e. g.).

In analogy to Symbols 2 and 3 which represent two categories of degree of decrease, partial and absolute, two sets of symbols have been provided for coding actions on the pathology state coded in Field T-2, one for complete return to normal (Symbols J, K, and L, described above) and one for partial return to normal (Symbols M, N, and Ø).

Thus, Symbols M, N, and Ø are used exactly as Symbols J, K, and L, except that they indicate that the test compound has not succeeded in bringing the organism back completely to its normal state.

When Symbols J, K, and L are used in Field T-1, evaluation in Field Y is made on the basis of complete restoration of normalcy (analogous to the complete abolition of a biological condition or process indicated by Symbol 3), as described in Division 8. When Symbols M, N, and Ø are used, evaluation is made on the basis of incomplete restoration of normalcy (analogous to the action indicated by Symbols 1 and 2), i.e., on the basis of degree of recovery as described in Divisions 6, 7, and 8.

17. Symbols P, Q, and R; coding of the test compound's exacerbative action on a pathological state or process, coded in Field T-2 as a symptom of a disease coded in Field E

Reference should be made to the preceding division which discusses the coding of pathological states treated by test compounds (Field E and T-2) and the coding in Field T-1 to indicate the test compound's action on those pathological states. The use of Symbols 1, 2, 3, J, K, L, M, N, and Ø for this purpose is explained in that division.

Symbols P, Q, and R complete the three sets of symbols that are provided for coding test compound's actions when the entry in Field T-2 is a term expressing a normal biological state or physiological process (but a state made abnormal by a pathology coded in Field E). The two sets, (1) J, K, and L and (2) M, N, and Ø, are used to code the compound's ameliorative action, whereas Symbols P, Q, and R are used to code the compound's exacerbative action. While the use of Symbols P, Q, and R may be relatively infrequent, they are included to present the total concept of coding Field T-1 under the circumstances of Field T-2 being coded with a pathological symptom indicated only as a normal state or process.

Symbol P is used when the test compound decreases the biological process which is in a pathological state and, in decreasing it, exacerbates the state, indicating that the process coded in Field T-2 had been in a pathologically depressed state when treated.

Symbol Q is used when the test compound increases the biological process which is in a pathological state and, in increasing it, exacerbates the state, indicating that the process coded in Field T-2 had been in a pathologically elevated level or accelerated pace when treatment was administered.

Symbol R is used when the test compound has made further aberrant an organism's activity or physiological balance which had been in a disturbed state at the time of administration; e.g., a disturbed nitrogen balance or abnormal behavior. Thus, Symbol R used in Field T-1 with Symbol 55 in Field T-2, for example, would indicate that the organism's behavior which had been abnormal at the time of administration was made even more abnormal (i.e., exacerbated) by the administration of the test compound, an exacerbative action that would be inadequately expressed by the terms "increase" or "decrease".

18. Coding of the test compound's failure to produce a response when the test was not made for specific action on any specific, named biological state or physiological process

Coding of the compound's failure to produce a response (negative data) is discussed in Division 1 of the Specific Directions and Explanations for Fields W, X, and Y. Most frequently, an experiment is designed with the objective of determining a compound's ability to perform one or more stated, specific actions. When the compound proves inactive with respect to a specific action, coding of that inactivity is properly restricted to that specific action, which means that Fields T-1 and T-2 are to be coded to indicate the action and biological state or process with which the test was concerned and the inactivity of the test compound with respect to that specific action and biological state or process is indicated by appropriate coding in Fields W, X, and Y.

Occasionally, however, negative test results are expressed as a generality; i.e., the author merely indicates that the test compound caused "no response". These are not unimportant data, even though it makes no reference to any specific action or specific biological state or process. To make possible coding this indefinite expression, a special symbol is provided in Field T-1, Symbol 0, which indicates that no biological action (increase, decrease, initiation, etc.) by the test compound was detected in a test for which the alteration of no specific biological state or physiological process was being sought.

Since the expression, "no response", entails no specific biological state or process, a special coding provision is also made for Field T-2, Symbol 1. This symbol in Field T-2 means essentially that none of the biological states or processes indicated by other Field T-2 symbols were affected by the test compound.

Thus, Symbol 0 of Field T-1 must never be used when a symbol other than 1 is in Field T-2 and, in the reverse, when Symbol 0 is in Field T-1, only Symbol 1 can be used in Field T-2. All other negative data (involving specific action on specific biological states or processes) must be indicated by appropriate coding in Fields W, X, and Y, as explained in Specific Directions and Explanations for those fields (Division 1, Subdivision B).

When Symbol 0 is used in Field T-1 and Symbol 1 in Field T-2, Field W must be coded with Symbol L or M, Field X with Symbol 01 (or possibly Symbol 02), and Field Y with Symbol 1.

Note that when a specific biological state or condition is named as being one for which the test compound is administered to affect and when the test compound might affect that biological state or process in either of two ways (increase or decrease, antagonism or synergism of a secondary compound's action on it) and it caused neither action, Symbol 0 should never be used in Field T-1 to code the inactivity on this specific biological state or process. Instead, Field T-1 is double-coded with both symbols (indicating both possible actions the test compound might have had, 1 and 2, or 8 and 9), Field T-2 is coded with the specific biological state or process, and Fields W, X, and Y are coded to indicate the negative activity.

19. Symbols available for expansion of Field T-1

Symbols B, H, and I are available for actions other than those of the present list of Field T-1. Symbol B was assigned earlier to an action described as "summation", but because of a general lack of use and misunderstanding of the meaning and use of the term, it has been omitted in the present list, freeing Symbol B for another use. Symbols D, E, F, and G may eventually be found to be used so infrequently that their present definitions could be replaced by others more useful.

Having assigned to the IBM 0 zone punch the definition "no effect" (when no specific biological state, character, or process had been tested for its response to the test compound), Symbols S through Z are not available. Since the actions already included in the list have been adequate for all data encountered by the CBCC, it has not seemed probable that Symbols S through Z would be needed.

20. File of coded biology data arranged according to symbols for test compound specific actions

The CBCC has established no separate file of biology data arranged according to the actions coded in Field T-1. The most probable use of such a file would be in assembling antagonism or synergism data, but it has so far been more practical to depend on the special file arranged by Field D entries (the secondary compound file), performing a machine sort for synergism or antagonism coded in Field T-1, rather than maintaining a separate Field T-1 file which would necessarily be as large as the principal file arranged by CBCC Chemical serial number, due to every line demanding an entry in the field.

21. Double coding in Field T-1

Two code entries are never permitted in Field T-1, with the one exception explained in the section dealing with coding of no effect on a specific biological state, character, or process coded in Field T-2 when the compound might have caused effect in either direction (when both Symbols 1 and 2 are coded in Field T-1 and Fields X and Y are coded to indicate the failure to cause either an increase or decrease); refer to Division 18. When both Symbols 1 and 2 are coded in Field T-1, both are punched on the same IBM card in Column 57.

BIOLOGICAL STATE, QUALITY, OR PROCESS ACTED ON OR PRODUCED BY THE TEST COMPOUND OR SECONDARY COMPOUND

Organization

The four columns of Field T-2 provide four organizational levels of types of states, qualities (characters), or processes, from the most general type (indicated by the symbol of the first column, Column 58) to the most specific type (indicated by the symbol of the second, third, or fourth column, Columns 59, 60, or 61, according to whether the symbol is of two, three, or four units). The most general of these states, qualities, or processes, therefore, has a symbol of only one unit, to be coded in Column 58. For example, Symbol 1 represents an unspecified gross effect, Symbol 2 represents general unspecified growth and differentiation which can be affected by the test compound, Symbol 8 represents unspecified gross activity of tissues, cells, or fluids which activities can be affected by the test compound. By the very general character of the definitions for these single-unit symbols, it will be understood that they are seldom actually used, because biological response to a test compound ordinarily involves a more specific state or process. In the list of Field T-2 items, the single-unit symbols serve principally to define the several general categories of states and processes. To date, Field T-2 has twelve of these general categories, represented by Symbols 1, 2, 3, 4, 5, 7, 8, 9, A, B, C, and F.

The more specific states, qualities, and processes which fall under the twelve categories are designated by symbols of two to four units, according to their natural relationships. Several major categories of cardiovascular processes or conditions, for example, are listed, all of which have symbols whose first unit is the letter C and a second unit unique to that specific major cardiovascular process; for example, cardiac rate, Symbol C1; amplitude of heart beat, Symbol C2; circulatory rate, Symbol C6; etc. Under each of these general cardiovascular states or processes, are organized those that are more specific. Thus, under general cardiac rate, Symbol C1, for example, are auricular states and processes (Symbol C11), ventricular states and processes (Symbol C12), pacemaker and conducting abnormalities (Symbol C13), etc. Finally, the fourth column permits categories of a fourth level of specificity, such as those items under auricular states and processes (Symbol C11): auricular premature contraction (Symbol C111), auricular tachycardia (Symbol C112), auricular fibrillation (Symbol C113), etc.

Because certain states and processes show relationship to more than one of the categories by which the Field T-2 items are organized, an occasional item is entered twice, once with the group with whose symbols its symbol belongs and again with the group with which it has another natural affinity. For example, both of the pathological states, collapse and syncope, are assigned symbols of the toxicity series, 115-, and are listed with that series as 1154 and 1155; a coder might search for these states, in order to get their code symbols, under the category of items dealing with body fluids, particularly the items of blood volume, so collapse and syncope are also listed (with their symbols, 1154 and 1155) with the items whose symbols are 87--. An alphabetical list of the Field T-2 items was constructed for CBCC coding and it was useful, but only as a supplement to the list as it is presented in the Code here. The alphabetical list proved unable to replace the naturally-arranged list partly because it is difficult, for such an alphabetical list, to include each item defined in all the ways it might occur to a user to search for it. Unfortunately, coders have a tendency to use the alphabetical list without making an accompanying reference to the list arranged by natural association of items, leading to errors in selecting the exact code symbol, because the alphabetical list does not have all related items listed together to permit scanning for the most appropriate choice.

General Use

The general use of Field T-2 is distinguished in the Key section describing Field T in general (Fields T-1, T-2, and T-3). The field is used to code the specific biological state (e.g., death, Symbol 11, 111, or 112; dormancy, Symbol 2D1; shock, Symbol 117; tolerance, Symbol 51; cyanosis, Symbol 874; sinus arrest, Symbol C135), biological quality (i.e., a character, such as size of fruit, Symbol 192; nuclear shape, Symbol 226; blood cell number, Symbol 851), or biological process (tissue

regeneration, Symbol 272; atrophy, Symbol 411; tumor growth, Symbol 44; excretion, Symbol series FF--) which the test compound is tested to affect or cause. Whether the test compound is tested to affect or cause the state, quality, or process coded in Field T-2 is indicated by the coding in Field T-1.

If all the coding fields are considered in rank of importance, it is Field T-2 and Field T-1 that must be given first place along with the code identification of the compound tested. Every line coded must have an entry in Fields T-1 and T-2. Next in rank are the identification of the biological system tested (Field E and frequently Field J) and evaluation of the test results (Fields W, X, and Y), both of which the CBCC also considers essential information for every code line.

Specific Directions and Explanations

1. Use of symbols with fewer than four units

When a symbol of Field T-2 has only one unit, it is to be coded in Column 58 and the remaining three columns must be cross-hatched, as in the case of uncoded columns of Field E and Field J. Similarly, if the symbol has only two or three units, the final two columns or the final column of the field must be cross-hatched. This provides subsequent assurance that the coder did not err in omission, but intended to use only the first one, two, or three columns, as the case may be.

2. Use of Symbol 1; gross response

All of the Field T-2 items whose symbols begin with 1 are described as being "gross effects" which do not fit precisely with any other of the established categories of the field.

When the number 1 is used alone as a symbol (in Column 58), it is to code a generality, referring to no specific biological state or process nor even a specific type of biological state or process (frequently, if the response is of a specific type, it can be indicated by a symbol of Field T-3, using Symbol 14 in Field T-2); consequently, Symbol 1 is never used except with negative data which are described as such a generality. (Positive data expressed as this generality would not be coded by the CBCC; for example, a statement such as, "the test compound produced response", with no indication what the response, or type of response, was, would be meaningless and would not be coded.) In other words, only when an author states that "no response" occurred and does not specify that one or another specific biological state or process or specific type of response was not affected or caused, can Symbol 1 be used. It is used only with Symbol 0 in Field T-1 which is itself restricted to this one use with Symbol 1 of Field T-2. (See Division 18 of the Specific Directions and Explanations of Field T-1.)

3. Coding of DEATH of organisms as a response to a test compound; restrictions on the use of Symbols 11, 111, and 112 for coding death

Those specific responses that can be considered as general toxic responses and which do not conveniently fit with other pathology categories of Field T-1 are coded by the symbol series 11-.

The first of these responses is death which is somewhat unique in the list of Field T-2 items in that three definitions and three symbols have been assigned to it, each differing in terms of conditions leading to death. The test compound's potency for inducing death is such important information that Field T-2 has been given certain distinguishing functions it ordinarily doesn't have, to which end have been provided the three definitions for death; the three definitions permit the field to distinguish certain information about the dose and its administration. For example, the duration of administration is given a gross distinction by Symbol 112 which bears in its definition the stipulation that administration was continuous for over 24 hours. In contrast, Symbols 11 and 111 both differ from Symbol 112 in that, by their definitions, administration is either by a single dose or, if continuous or multiple, can be no more than 24 hours. Such distinction is ordinarily exclusively the function of Field P and, even in the case of using Symbols 11, 111, and 112, Field P is used to indicate the duration of administration more precisely than >24 hours, 24 hours, or <24 hours. Such minor distinctions made by Symbol 112, as indicated by this example (frequency of administration, duration of administration, or time to kill) are not actually of much significance as a means of sorting for coded data, since that particular information is coded in special fields (Fields O, P, and U). However, by the collective distinctions made in frequency of administration, duration of administration, and killing time, Symbol 112 is useful in

distinguishing potencies of test compounds for causing death, implied by the terms "chronic" and "acute", as defined hereafter. Having Symbol 112, in addition to 111 and 11, permits Field T-2 to have uniquely, in the case of coding "death", the general function of distinguishing the degree of severity of action (the degree of potency) of the test compound.

When a test compound, at a given level of administration, causes death only after a considerable time, the response is referred to as "chronic"; if, at a given dose, the test compound causes death in a relatively short time, the response is said to be "acute" or severe. Very commonly, when these determinations are made for a compound, they are spoken of as "chronic toxicity" and "acute toxicity" determinations. In spite of the frequency of usage of the latter terms in certain biological fields of testing, they are somewhat unfortunate in that the word "toxicity" is not itself a synonym of "death". The fact that it can refer to any of a large number of non-lethal detrimental effects frequently leads to confusion especially with coders who have had no reason to use the terms, or encounter the terms used, synonymously with "death" determinations.

Drawing an arbitrary line at the 24-hour point, then, any death produced within the shorter time period (24 hours or less) might be referred to as "acute toxicity", whereas death produced only after 24 hours is referred to as "chronic toxicity". This is somewhat modified, however, by the provision that when death is caused from a single administration (not continuous and not multiple), the severity should be considered as acute regardless of the time taken to kill (< 24 hours or > 24 hours). Note that these distinctions are made by the CBCC; there are probably no such universally accepted exact demarcations between acute and chronic toxicity. However, having Symbol 112 does have one important "cataloging" advantage; it makes a convenient coding distinction whereby all compounds of higher potency for lethal action can be separated from those having lower potency for lethal action. Potency of a compound for causing a given response such as death is always indicated in Field Y (or indicated by the combined coding of Field Y and Field M or N). The significance of making a gross potency distinction in Field T-2 is that, by having done so, the Field Y evaluation may subsequently be made on the basis of only one or the other of the two broad categories of lethal potency. In other words, evaluation of Field Y is an expression of either the "degree of acuteness of lethal potency" or the "degree of chronicity of lethal potency", rather than merely the "degree of lethal potency".

In the fifth mimeographed edition of the Code, Symbol 11 was defined appropriately merely as general toxicity (and, under it, were organized the various more specific toxicities such as death [111 and 112], local toxicities [113], systemic toxicities [114], etc.). In the sixth edition and in the present list of Field T-2, Symbol 11 has been utilized to code death specifically rather than to code general toxicity, a rather exceptional arrangement which exists only for the historical reason just explained. The present definition of Symbol 11 provides another distinction to be made for death (just as Symbol 112 provides a distinction as described above) which is not made by any other field, though it resembles the type of information coded in Field S-3. It is a distinction that ordinarily need not be made if administration is made separately to each individual tested (in which case the dosage given to the individual is ordinarily determined), but is a distinction that needs to be made when administration is to a group or population of individuals or when it is to one or more animals consuming the test compound ad lib. In the latter situations, acute toxicity may be expressed only in terms of the time taken to kill the organisms tested under the conditions of administration, but there is no determination of the amount of the compound the individual actually consumed or contacted. This latter information is of greater basic biological significance than merely information about the amount needed in a field spray or in a food material, or in an aerosol, etc., to accomplish a given percentage of kill. Whenever the data tell nothing more than the lethal amount applied to a population (without having determined the amount received by each individual), Symbol 11 is used and the dose coded in Field M or N is the dose administered to the group, population, or environment (food, etc.). Symbol 111 is used only when the amount received by each individual and causing death in that individual is determined and coded in Field M or N.

This last distinction is only made when death occurs in 24 hours or less (acute toxicity, Symbol 111 or 11). For death caused only after 24 hours (chronic toxicity, Symbol 112), no similar distinction is made as to whether or not the dose received by each individual has been determined. An additional symbol might be added to make the latter distinction, but it is not a refinement the CBCC has found necessary in the case of "chronic" lethal effects.

Death may be either a desired or an undesired response of a given organism to a chemical. In the case of parasitism and pathogenicity, a complex situation exists in which death is ordinarily desired for the parasitic organism and at the same time is ordinarily unwanted in the host. It is necessary to make some distinctions relative to these aspects and the use of Symbols 11, 111, and 112, explained as follows.

Symbols 11, 111, and 112 are used when the intent of the test is to find compounds that will kill an undesired test organism (e.g., rodenticides, molluscacides, herbicides); these symbols are also used when the intent of the test is to find compounds that are safe for a test organism (i.e., safe for administration for another purpose such as therapy). However, in the case of the parasite-host relationship, Symbols 11, 111, and 112 are never used when the intent of the test is to determine the compound's ability to kill the parasites; instead, Symbols of the 17-- series are used to indicate that the host has been relieved or freed of the parasite or the pathogen by the latter's death due to the test compound.

4. Symbols 11, 111, and 112 vs. Symbol 1812; death of larger organisms vs. death of microorganisms due to the test compound or secondary compound; a discussion of reasons for this coding distinction

The last sentence of the preceding division has pointed out that death of any pathogenic organism or parasite due to the test compound or secondary compound while the pathogen is in its living host is not coded by Symbol 11, 111, or 112, but only by symbols of the 17-- series. (See Division 13.) A further exception is the death (or, at least, a reduction of the population) of arthropods infesting living hosts, which is not coded by Symbol 11, 111, or 112, but only by symbols of the 13-- series. (See Division 10.)

Finally, the CBCC restricts the use of Symbols 11, 111, and 112 by never using the symbols for coding lethal action on any microorganism, parasitic or not. (See Division 14.) This general rule has been observed even though no guide has been constructed for coders specifically designating size limitations by which organisms will be defined as "microorganisms". Lethal action on microorganisms is coded by Symbol 1812 (if the organisms are treated while on a non-living host) or it is coded by Symbols 171 and 1711 (if the organisms are on a living host).

The separation of lethal actions on all microorganisms came about as the result of Field T-2 having been developed from lists of biological responses compiled separately for the various biological disciplines, pharmacology, pathology, microbiology, plant physiology, etc. The microbiological items naturally included "cidal" actions of test compounds on bacteria, fungi, viruses, etc.; in the list of biological responses prepared for pharmacological and agricultural considerations, lethal action was included, but with the emphasis on determinations of safe therapeutic levels as well as killing potency ("toxicity" data), for larger animals and plants; items of the pathology list were concerned basically with therapeutic actions including destructive action or any infectious microorganisms as causes of treated pathologies. For microbiology, Symbol 18 was established for coding effects, including death, demonstrated to be specifically on microorganisms whether pathogenic or not and whether or not they were in or on a living host. For pharmacology, the symbols of the 11-- series (111 and 112) were established for death. The 17-- symbol series was established for coding ameliorating effects on diseases and, if the disease were an infectious disease, this was equivalent to coding at least a suggestion of toxic or lethal effects on pathogenic microorganisms in their host.

With the sixth mimeographed edition of the Code, the symbols of the 18-- series were changed to their present definitions, rephrasing the definition for Symbol 171 so that it was (and is) to be used for any lethal effect demonstrated on a pathological microorganism while it is in or on its living host; this leaves for the definitions of symbols of the 18-- series toxic effects on any microorganism not on a living host.

For the present edition, no change has been made from the original provision separating data of lethal action on microorganisms (series 18--) from the "toxicity" data (series 11--), partly because so much information has been coded and punched for CBCC files using these symbols that the task of retrieval and correction would be prohibitively great.

In programming a retrieval of toxicity data from the punched card files, the CBCC invariably makes the initial sort on the basis of taxonomy. In other words, instead of removing from the files all cards coded with "death" in Field T-2 and subsequently sorting for the organisms relevant to the correlation study, the cards are removed which have coded on them the organisms desired and from these are sorted the cards coded with "death" in Field T-2. Thus, the coding distinction that the two groups of symbols is intended to make in Field T-2 (11-- vs. 18-- and 17--) has so far proved to have little retrieval value and whatever advantage it may pretend is outweighed by the confusion it has caused coders.

For these reasons, it is suggested that, for a new coding project, consideration be given to coding "death" caused by the test compound (or secondary compound) by only a single set of symbols (i.e., death of all vertebrates, invertebrates, and plants), except that lethal effects on pathogenic organisms in the living host (representing a specific disease) should probably continue being coded as one of the ameliorative effects on pathology (i.e., with the 17-- symbol series) and lethal effects on populations of special taxonomic groups should probably be coded separately, as the 13-- symbol series does for arthropod infestations of living hosts, when the nature of the information collection indicates it would be an advantage.

5. Symbols 11, 111, and 112 are never used with Symbol 3 of Field T-1 to code prevention of death; only Symbol 7, 8, 9, or A of Field T-1 may be used with death coded in Field T-2

Chemical tests on biological systems may involve "death" (considered as a biological state) caused by agents or conditions other than the test compound or secondary compound. In such tests, the test compound or secondary compound may be administered as a preventive to the state of death caused by pathologies which in turn were caused by agents or conditions other than the test compound or secondary compound.

According to its definition, Symbol 3 of Field T-1 can be used to code the test compound's prevention of either a naturally occurring process or a pathological symptom coded in Field T-2. HOWEVER, its definition also stipulates that Symbol 3 is never used by the CBCC to code prevention of death (Symbols 11, 111, 112, and 1812). The coding of effects on death due to pathology (e.g., hastening or delaying death) is accomplished only by use of symbols of the 16-- and 17-- series of Field T-2, as explained in Divisions 9 and 13. As a consequence, the restriction is placed on Symbols 11, 111, 112, and 1812 that they are used only for coding death caused by the test compound or secondary compound, and only Symbol 7, 8, 9, or A of Field T-1 may be used to code this. Symbols 1 and 2 of Field T-1 are never used with Symbol 11, 111, 112, or 1812, because the increase or decrease of death in an individual (or in a colony of microorganisms, regarded collectively) is not reasonable; death can only be "produced" (Symbol 7 of Field T-1) in an individual. In a group of individuals (or a group of colonies of microorganisms), increase or decrease of death would describe the test compound's effect on an existing death rate due to a factor other than the test compound; if this other factor is a secondary compound, the test compound's effect on that death rate (incidence) caused by the secondary compound would be coded by Symbols 8, 9, or C instead of Symbols 1 or 2; if the other factor were any other pathology than a secondary compound's effect, the test compound's effect would be coded as preventing death (permitting survival) of a percentage of the group of individuals (or colonies of microorganisms), using Symbol 1754 (or 1711, 172, or 1752) of Field T-2, rather than Symbol 11, 111, 112, or 1812.

6. Symbols 11, 111, and 112; explanation for coding such effects as death as STATES (Field T-2) CAUSED (Field T-1)

With certain of the Field T-2 items, the use of Field T-1 (or at least the use of two fields, T-1 and T-2) may appear unnecessary and seem to represent a redundancy. The items particularly concerned are a few of those which, by their nature, can be "caused" by the test compound or secondary compound. Thus, such states as death (Symbols 11, 111, 112, and 1812), relief (symbols of the 13-- series and 17-- series), exacerbation (symbols of the 16-- series), irritation (Symbol 1131), dehydration (Symbol 875), and discoloration (Symbol 416), when caused by the test compound could be expressed in English adequately merely by saying that the test compound "kills", "relieves", "exacerbates", "irritates", "dehydrates", or "discolors".

It will be observed that this is not the case with most Field T-2 states, however. Most of the Field T-2 states can be expressed in English as having been caused by (1) specifically naming the

state (Field T-2) and (2) combining it with the non-specific verb "cause" (Field T-2); (e.g., the test compound "causes rigor", "causes edema", "causes coma", etc.). For coding these latter effects, it is not difficult to see why Field T-1 is coded with Symbol 7 and Field T-2 is coded with the specific state or condition.

Most of the states or conditions of Field T-2 can not only be caused by the test compound, but they can be caused by other agents and factors and treated by the test compound. The symbol for any state in Field T-2 can be combined with any specific action on that state (Field T-1), whether the action is initiation, intensification, diminution, or abolishment. For this reason, the test compound's effect is always coded by naming the state or condition in Field T-2 and indicating in Field T-1 whether it is caused or affected, even in cases for which it might be possible to express it by a single verb. Therefore, the fact that a test compound "relieves", "prevents", or "cures" a disease, or "irritates", "dehydrates", or "discolors" a test organism is always coded as the test compound's "causing relief", "causing cure", "causing death", "causing irritation", etc., obviating any troublesome exceptions for coding verbs in Field T-2 ("irritates", "dehydrates", "discolors", etc.) or to add these specific verbs to Field T-1 where the number of symbols available is very limited.

The concision that would be afforded using a single term (i.e., the verbs "kills", "relieves", "cures", "irritates", etc.) is sacrificed to the coding pattern which must be used for the majority of effects ("causes rigor", "causes edema", etc.) and which must be used for coding test compound effects on a secondary compound's causing death, relief, cure, irritation, etc.

7. Symbols 113- through 117-; non-lethal toxicity (general pathological states other than death); local toxicity (symbol series 113-) vs. systemic toxicity (symbol series 114-); paralyses (symbol series 115-); convulsions (symbol series 116-); shock (symbol series 117-)

All of the symbols of series 113- through 117- are defined as morbid states other than death. Although the use of these symbols is more frequently for coding conditions caused by the test compound (the use for which these particular symbols are principally intended), they are used also to code pre-existing symptoms of a major disease coded in Field E, when that symptom is specifically treated or affected by the test compound.

The 113- series of symbols consists of conditions that occur as morphologic disturbances at any given site coded in Fields H and I. The 114- series of symbols are conditions that involve the entire body or are too general in concept to be defined as concerning a given site, including subjective sensation and symptoms which, though they may vaguely involve certain limited parts of the body, do not involve morphological damage in the same distinct way as the items of the 113- series. The three symbol series, 115-, 116-, and 117-, represent types of paralyses, convulsions, and shocks, respectively.

8. Acute systemic toxicity (Symbol 1141) vs. side effects (Symbol 1142); coding of side effects

Essentially, the difference between the definition of 1141 and that for 1142 is one of degree, 1141 being for systemic effects of most severe intensity. The use of Symbol 1141 is ordinarily dependent on the author's description of the condition as being of such intensity. Symbol 1142 is also a symbol for any of a large number of systemic morbid conditions (i.e., it is used for non-specific coding of systemic toxicity), but only when the condition is of a comparatively mild, less acute degree.

Instead of Symbol 1142, there might be listed all of a large number of general and common toxic symptoms caused by the test compound or caused by a disease and collectively treated by the test compound, such as headache, dizziness, nausea, vomiting, etc. If this were the case, the CBCC coding procedure would require, whenever any such symptoms occurred, a separate code line for each one. Since many pathological conditions caused or treated by the test compound involve more than one and frequently several of these symptoms, the number of code lines necessary to code information about all these commonly occurring subjective symptoms would be prodigious, particularly in the case of clinical data. The effect of a test compound on such secondary symptoms common to so many major pathological states or its effect in producing the secondary symptoms is of comparatively minor significance and the CBCC has refrained from coding them or from providing specific symbols for them, coding any or all of them collectively and non-specifically with Symbol 1142. Even the production of pain is not coded; a symbol for pain, Symbol 9B8, is used only when the compound may be shown to affect the sensation as an anesthetic, when the effect is measured by well-defined and measurable motor responses

of the test animal. When Symbol 1142 is used, however, the specific side effects should be designated in the written abstract of Field T-2.

In spite of the general restriction for coding a side effect (as defined above), specifically and with a separate code line, the CBCC may occasionally make exception when the toxic symptom treated or produced seems to be a particularly significant response to the chemical or when the symptom's response, when treated by the test compound, seems especially significant.

When the compound produces death (Symbol 11, 111, or 112), there are frequently more or less severe toxic manifestations immediately prior to the actual death (i.e., symptoms related to and accompanying death). The coding of such death-accompanying responses would require, for each, a separate code line, or several separate code lines, in addition to the line coding death itself. The CBCC prepares only one code line, the line for the lethal response. Any responses that typically accompany the death due to the specific test compound are to be included in the written abstract of Field T-2 of that line coding the death of the organism.

9. Symbol 12; viability

Symbol 12 has had a checkered career in the CBCC Code, partly due to the confusion arising from the fact that both an organism's "viability" and its "survival of lethal pathology" are associated with death which treatment with a test compound can affect (delaying, speeding, or preventing death's occurrence). For this reason, there has been a tendency to attempt coding both of these with a single symbol, Symbol 12. Reference should be made to the discussion of survival of lethal pathology, Symbols 1753, 1754, 1621, and 1631, in Division 13. The term, "viability", is not used to express an organism's survival of pathology, but describes an organism's ability to survive normal environmental conditions. For example, the term is applied commonly to plant seeds in describing their ability to survive seed dormancy and germination under normal conditions. The effect of chemical treatment on viability is most frequently in terms of a percentage increase in number of organisms (as seeds or spores, e.g.) growing or persisting when treated, though it might conceivably be in terms of increase in duration of survival time. For example, chemically treated seeds might germinate in a higher proportion or they might withstand storage longer without losing viability.

An organism's viability might conceivably be regarded as analogous to that of surviving a pathology in that low viability which is responsive to treatment can be reasoned to be due to some detrimental environmental factor (etiological to a pathological state) which chemical treatment can affect. Nevertheless, it has seemed more reasonable to circumvent the technicality of a somewhat artificial association of pathology with "viability" by coding in Field E the organism treated with the test compound and coding Field T-2 with the term viability which, in the restricted sense defined in the Code, implies only the organism's ability to survive under normal conditions. When the organism is described as exposed to some specific, named factor which proves lethal to the organism when unprotected by treatment with the test compound (even one of the normal environmental factors such as heat, cold, radiation, drying, moisture, low O_2, etc., in excess), its ability to survive should not be coded by Symbol 12, but the pathology associated with the specified detrimental factor should be coded in Field E and the effect of the test compound on the death of the organism due to the specific detrimental factor should be coded by Symbol 1621, 1631, 1753, or 1754. If the effect of the test compound is preventive of the pathology rather than effecting death due to the pathology, use a symbol of the 178- series.

10. Symbols 131 and 132; coding of REDUCTION OF INFESTATIONS BY ARTHROPODA due to test compounds

Tests in which application of the test compound is made to an infestation of arthropods on their living host presented such a consistent coding problem that finally a special series of symbols has been provided for coding the data. The special aspects of these tests which made the results seem unsuitable for being coded with symbols of the 11--, 17--, or 18-- series will be reviewed briefly.

First, the test compound's reduction of the arthropods is frequently not actually known to be due to death of the insects; especially in field tests, the reduction might have been the result of repellent action. A second aspect is the fact that so little control is afforded by the method whereby application is made to a population (infestation) of arthropods en masse that the data offer little

evidence of the compound's lethal effect on the individual, since there is frequently no way of determining the quantity of test compound that reached the individual. Both of these aspects contributed to a reluctance to code the arthropod response with any of Symbols 11, 111, and 112.

A third difficulty arose from the way in which the results of such tests on arthropod infestations are frequently expressed. While the effect might be expressed in terms of the percentage reduction of the arthropods, it is frequently expressed in terms of the percentage of the hosts or host cleared of arthropods. In the case of infectious pathologies, such an effect expressed in terms of the host is coded only with symbols of the 17-- series; originally, this was the only existing way to code the test compound's clearance of the host of an arthropod infestation, inasmuch as symbols of the 18-- series were restricted to organisms on non-living hosts. However, the CBCC was reluctant to regard these insect infestations of living organisms (ordinarily infestations of plants) as being diseases of the living organism and to code the amelioration of infestations by insects with symbols of the 17-- series. This was in part because insect damage to organisms, while academically representing pathology by the fact of the damage, does not fall within the general concept of disease entities caused by microorganisms and true parasites, in the same way that wounding of a man or other animal by a dog (to draw an exaggerated analogy) is not ordinarily regarded as being diseased by the dog. Furthermore, so many data are available from insecticide tests falling within this description that at one time it seemed likely they might lead to engorgement of the 17-- symbol category in the punched card files, to the ultimate detriment of retrieval facility.

As a solution to this dilemma, Symbol 13, 131, and 132 have been introduced for such arthropod tests.

Observe that the definitions do not specify "death", but only reduction of the infestation. This does not mean that if death is demonstrated to be the cause of the reduction of infestation, Symbol 13, 131, or 132 can not be used; death produced in insects infesting living organisms when treatment is given to the infestation is never coded by Symbol 11, 111, or 112.

Occasionally, the manner of treatment plays a role in determining whether to use symbols of the 13-- series or Symbol 11, 111, or 112, even when an arthropod is on its living host; if the "infestation" is restricted to a single individual or a very few individuals and if administration is by some method directly to that arthropod and only to the arthropod individual, any lethal effect to the arthropod should more reasonably be coded with Symbol 11, 111, or 112 than with Symbol 131 or 132. This is suggested because such a treatment so little resembles a treatment designed specifically to affect an infestation, but more nearly resembles a test for the individual's vulnerability to the test compound. Such a situation might conceivably exist when the individual arthropod is maintained on its host only because the arthropod is of such a nature that its normal existence is dependent on remaining in contact with its living host.

The symbols of the 13-- series are intended to supplement Symbols 11, 111, and 112 and to be analogous to symbols of the 17-- series. Both of these series represent only a single direction of the action, the decrease of the test organism by its death (in the case of the 17-- series, this decrease is implicit by the definition of relieving the host of a pathogen). Therefore, symbols of series 13-- also are defined to indicate only a single direction of action, decrease of the arthropod infestation. This means that, as in the case of Symbols 11, 111, and 112, and symbols of the 16-- and 17-- series, Symbols 1 and 2 of Field T-2 are never used with the 13-- series, but only Symbol 7, 8, 9, or A of Field T-1. The probabilities of a test compound, selected for testing to reduce an arthropod infestation, acting in the opposite way (in some way facilitating or increasing the degree of arthropod infestation) are so remote that it has not seemed worth inserting a special symbol series to accompany the 13-- series for coding such an exacerbating effect in the way that symbol series 16-- has been included to accompany the symbol series 17--.

11. Symbol 14; coding of Field T-2 when the biological response is expressed by the author only in terms of one of the general categories of Field T-3

The purpose of Field T-3 is distinguished in the introductory section discussing Field T in general and described in the section dealing with Field T-3 specifically.

Occasionally, data are encountered in which the author expresses an effect only in terms of one of the general categories of response described by Field T-3 items. This does not necessarily represent data that are too vague or general to be coded; to the contrary, it most frequently is a precise description of response even though in a somewhat collective sense. For example, to indicate only that a test compound has proved to be sympathomimetic may be assumed to mean that the compound has been demonstrated to bring about all the specific effects typical of that category of drugs.

The CBCC codes such information by entering in Field T-3 the code symbol for the general category of chemical action and by use of a special symbol in Field T-2 which has no meaning other than to refer the interpreter from Field T-2 to Field T-3. This is Symbol 14 which is used only with Symbol 7 of Field T-1 to mean that the test compound causes a general effect as indicated by the coding in Field T-3.

Symbol 14 is not to be used by a coder merely because a specific biological state or process has not yet been included in the Field T-2 list; in this case, Field T-2 will need to be expanded by the Center's adding that item to Field T-2 and assigning it a symbol. Also, it will be understood that Symbol 14 can never be used without an entry in Field T-3.

12. Symbol 15; coding of a response involving an unspecified normal functioning of a specific anatomical part of the test organism

Occasionally, test results are expressed by an author only by stating that the normal function of an anatomical part has been affected (interrupted, increased, decreased) by the test compound (or by a secondary compound, which effect is itself affected by the test compound). It is not always certain, by such a general statement, which normal function of the anatomical part has been affected (if the part is known to have more than one specific normal function) or whether all its functions are affected. Although it is not frequent that the coder can not determine what specific process has been affected by having the anatomical part designated by the author, a means of coding a non-specified process of a specified anatomical part is needed.

Symbol 15 is provided in Field T-2 to indicate a normal process unspecified except by reference to Field H-1 or I where the organ or tissue is named whose normal (but unspecified) function has been affected by the test compound as indicated by coding in Field T-1.

13. Symbols of the 16-- and 17-- series; coding of the EFFECT OF test compounds ON basic pathological states (Field E) of the biological organism (in contrast to coding of production of pathological states [Field T-2] BY the test compound); only Symbol 7 of Field T-1 may be used with symbols of the 16-- and 17-- series; symbols of the 16-- and 17-- series are used to code chemical effects on any infectious or non-infectious pathology EXCEPT TUMORS

Compounds are very frequently administered to test their effects on pathological states of an organism. Field E is used to code the specific pathology treated, the symbols for pathology being listed as the Pathology Code section of Field E.

Coding of pathology is discussed in considerable detail in the section of the Key dealing with the Pathology Code of Field E. Whenever a compound is administered to test its therapeutic (or exacerbative) effect on a specific pathological state, that state must be coded in Field E. In other words, if a compound is tested therapeutically, Field E is never coded with the diseased organism treated (host), but only with the taxonomic symbol for the pathogen causing the infectious disease or the Pathology Code symbol for the non-infectious disease; the diseased organism is coded in Field J. Under these circumstances, Fields T-1 and T-2 are coded in one of two ways. They may be coded to indicate the effect the compound has on the disease in general in Field E, using any symbols of the 16-- or 17-- series in Field T-2 and Symbol 7 in Field T-1. They may, however, be coded to indicate the effect the test compound has on any one particular symptom of the disease in Field E, using the symbol for the specific pathology symptom in Field T-2 and any symbol other than Symbol 7 in Field T-1 (though Field T-1 Symbols 6, D, E, F, or G would not be appropriate for indicating a chemical action on a pathological symptom).

FIELD T-2
Columns 58, 59, 60, and 61

The effect of the test compound on a general disease coded in Field E is expressed in Fields T-1 and T-2. For example: the test compound "causes" (Field T-1) "relief" (Field T-2), "causes cure", "causes exacerbation", "causes prevention", etc. Division 6 discusses this terminology which may seem to be a redundancy, since these particular effects might be adequately expressed in English by a single word, a verb, (the test compound "relieves", "cures", "exacerbates", "prevents", etc.).

Symbols of the 17-- series are used only for coding chemical effects in relieving in some degree the diseased organism (coded as the host in Field J) or for coding prevention of the disease by the test compound (not for chemical action on any other preventive measure such as antitoxin, vaccine, etc.). Symbols of the 16-- series are used only for coding chemical effects in intensifying (exacerbating) the disease.

The CBCC has placed one arbitrary restriction on the use of symbols of the 16-- and 17-- series. Effects of the test compound on infestations by any arthropod are never to be coded by these symbols, except in the rare instance when the arthropod dwells internally in the host as a parasite and treatment must be given to the host similar to treatments of infectious pathologies. This essentially keeps the coding of effects on all arthropods acting as infesting organisms restricted to Symbols 11, 111, 112, and symbols of the 13-- series. Note that this does not mean that chemical actions on diseases affecting arthropods is not coded by symbols of the 16-- and 17-- series; it is only the effects on infestations by arthropods that are not coded by these symbols.

Since symbols of the 16-- and 17-- series are used only for coding effects on pathologies, it follows that the symbols are used only when the host in Field J is a living diseased organism. Coding errors occasionally occur due to attempting to use these symbols for indicating the effect on a micro-organism (particularly in the case of pathogenic microorganisms) when it is on a non-living "host" such as a non-living culture medium or on a non-living substrate other than a special culture medium. For effects on microorganisms on non-living hosts, symbols of the 16-- and 17-- series are never used, but only symbols of the 18-- series. (With symbols of the 18-- series, the action of the test compound is indicated, according to the usual coding pattern, in Field T-1.)

The coding of "death" caused by the test compound or secondary compound is discussed in Divisions 3, 4, 5, and 14. In these divisions, it is explained that death is coded by Symbols 11, 111, 112, and 1812 (Symbol 1812 being exclusively for death of microorganisms when on a non-living host). Symbols of the 13-- series are used to code a reduction of an infestation (restricted to arthropods) of a living host and although this reduction may involve death, the symbols are defined only in terms of reduction, without specifying whether it is the result of killing or repelling the infesting arthropod.

Of the situations in which death may be the test compound's effect, there remains (after the provisions afforded by Symbols 11, 111, 112, 1812, 131, and 132) the situation in which the test organism killed is a pathogenic microorganism or a parasite on its host. Death to these organisms under these circumstances is always coded by Symbol 171 or 1711, even though the symbols are not defined to specify that death is the cause of the reduction. (The probabilities are greater that reduction of the number of pathogens or parasites on a living host is a matter of their being killed than that reduction of the arthropod infestation of a living host [Symbols 131 and 132] is due to death.)

Because the definitions of Field T-2 symbols that are appropriate for effects on most pathologies are not also exactly applicable to or adequate for expressing effects on tumors, the CBCC has designated a special series of symbols for coding effects on tumors (Symbols 43 through 47, indicating association with biological states involving abnormal growth, Symbol series 4---). Therefore, when a tumor is coded in Field E, symbols of the 16-- and 17-- series are never used.

The expressions, "prevention of death due to a disease" and "survival of a disease", imply that death must be a typical or inevitable result of the particular pathology when untreated, otherwise administration would not be made with the objective of avoiding death. Exacerbative and ameliorative effects on pathologies which characteristically cause death when untreated are coded by distinct symbols, 1621, 1631, 1753, and 1754, when the results of the test are expressed in terms of an effect on the death (hastening or delaying death or increasing or decreasing the incidence of death).

No coding provision is made in Fields T-1 and T-2 for the expression "prevention of death (due to the disease in Field E)". The CBCC prefers interpreting this to mean that the diseased condition has

been cured or restrained and the effect is coded with Symbols 1711, 172, or 1752 in Field T-2. The definition of Symbol 1754 approaches the expression "prevention of death", since it is concerned with a decrease in incidence of death; as the Code indicates, however, Symbol 1754 should never be used unless for some reason it seems inadvisable to interpret the increase of survivors as being cases of curative or restraining action of the test compound. The CBCC never codes prevention of death by using Symbol 11, 111, or 112 combined with Field T-1 Symbol 3; Division 5 explains that Symbols 11, 111, and 112 have always been restricted for coding death caused by the test compound.

Although the CBCC has not made exception to the rule that Symbols of the 16-- and 17-- series should not be used when tumors are coded in Field E, it is recommended that consideration be given, for future use, to permitting Symbols 162, 1621, 1631, 1751, 1753, and 1754 to code effects on acceleration and retardation of the tumor (as contrasted to effects on increase and decrease in ultimate size of the tumor), and on death due to the tumor coded in Field E.

14. Symbols of the 18-- series; coding of effects of the test compound on the population of microorganisms on a non-living host

Symbols 11, 111, 112, and 113 through 117 in general describe toxic effects, including death, as they are produced in individuals. The symbols are never used to code death or toxic effects on a microorganism; in the case of tests on microorganisms, most determinations of toxic effects are expressed in terms of the effect on a mass population of the organism and these test results most frequently are in terms of effects on the normal growth of that mass.

Toxic effects on microorganisms are coded by symbols of the 17-- series, in the sense that, when the pathology treated by the test compound is an infectious disease, a cure (or reduction of number of individuals of the pathogen) represents a selective lethal effect on the pathogenic microorganism. However, since symbols of the 17-- series are restricted to coding effects on pathologies, the symbols are restricted to coding toxic effects of the test compound on pathogenic microorganisms in living hosts. This leaves need for a provision to code toxic effects of the test compound on non-pathogenic microorganisms and toxic effects of the test compound on microorganisms (pathogenic or non-pathogenic) on non-living hosts.

For this purpose, symbols of the 18-- series have been provided. The definitions of the symbols represent the microorganism's normal growth on any non-living "host".

Only three symbols are included in the list for coding effects on microorganisms on non-living hosts, 181 for general gross effects on the colony (i.e., any inhibition or facilitation of the colony's growth), 1812 for demonstrated lethal action, and 18 as an introductory symbol for the series which can be used if it is not known whether an inhibitory effect is a lethal effect or merely a repressive effect. (In inhibiting microorganisms, the action may be merely a repressing action [frequently described as a static action or stasis, e.g., "bacteriostatic"] or it may be a lethal action [a " 'cidal action", e.g. "bactericidal"].)

As in the case of Symbols 11, 111, and 112, only Symbol 7 is used in Field T-1 with death of microorganisms (Symbol 1812) in Field T-2; Symbol 1, 2, or 3 is used in Field T-1 with Symbol 181 of Field T-2, according to whether development is accelerated or caused to increase beyond normal limits (Symbol 1), retarded in rate or decreased to a smaller ultimate size (Symbol 2), or made static ("stasis"), i.e., restrained at the stage of development in which the colony was at the time of application of the test compound (Symbol 3).

15. Symbols for series 28-- and 2A--; formation and size change in organs and in the entire organism

The items of Field T-2 referring to development and ultimate character of organs (series 28--) and the organism (2A--) are most frequently used in cases of effects of test compounds on young, developing organs and organisms. However, the symbols are not excluded for use for mature organs and organisms, if the test compound has been administered to a mature organ or to the mature organism and change occurs which alters the weight or volume; in particular, Symbols 281, 2811, 2A1, and 2A11 might be used to code size or weight of the mature organ (281 and 2811) and organism (2A1 and 2A11).

16. Symbol series 29--; process of change from one distinct juvenile form to another and metamorphosis to the adult

The development of individuals of some species involves one or more specialized juvenile forms, each of which feeds and grows to its normal limits and is terminated by a morphological change, which may be abrupt or may involve a quiescent stage of anatomical reorganization, to a more advanced stage or the adult. The most remarkable of these are the developmental stages of arthropods, especially insects, each stage terminated with a molt or a quiescent stage, ending with the final juvenile form being graduated as the adult. The transition of aquatic juveniles of Amphibia to the truly amphibian adult is another example. The symbol series, 29, is for these metamorphosing processes of individuals from one developmental juvenile stage to the next.

Certain other organisms reach an adult form only after a series of juvenile generations, a series of which represent continually more advanced developmental stages to the adult generation. In the case of plants and some lower animals (in particular, the Sporozoa, Cnidaria [Coelenterata], and Trematoda), the product of sexual reproduction (the zygote) does not develop, as an individual, directly into an adult, regarding the stage capable of sexual reproduction as the "adult" stage; instead, the zygote develops into a wholly different type of individual whose structure and mode of existence frequently differs radically from its parent and which reproduces asexually. (In some species, the offspring of this asexual reproduction develops into still a third different type, also capable of reproducing only asexually. Even more intermediate forms may occur in some species.) While this asexually-reproducing generation is so prominent in the life cycle of many organisms that it has resulted in the popular concept of an "alternation of generations", the one or more asexually-reproducing generations of Sporozoa, Cnidaria, Trematoda, and plants in general actually should be regarded as very elaborate juvenile forms. In the case of the higher plants, this elaboration has reached such a level that the "adult" is reduced to the most simple proportions, essentially remaining enclosed in the sporophyte (the asexually-reproducing "juvenile" generation). These elementary facts are reviewed only to assist in drawing the distinction between the point of change in form of a developing individual (e.g., Insecta) and the point of change of form when reproduction is involved in progressing from one developmental stage to the succeeding stage (e.g., Sporozoa, Trematoda, and plants).

In the case of species having no "alternation of generations", the general process of development of any individual, from zygote to adult, is coded by symbols of series 2A--, regardless of whether its development involves one or more special juvenile transition processes coded by symbols of series 29--. The general final process of assuming adult characteristics by any individual is coded by Symbol 2B, but when the test compound effect is expressed as being specifically on metamorphosis processes which end with the adult insect or amphibian, Symbol 29 should be used.

In the case of the species described above whose developments or life cycles involve a series of juvenile generations (an alternation of generations), the general process of development of any individual from the zygote to the mature asexually-reproducing stage typical of that particular generation (i.e., of that particular juvenile form), or of any individual from the bud, spore, or point of cell fission to the mature form typical of that asexually-reproducing generation, or to the mature sexually-reproducing "adult", is coded by symbols of series 2A--. The process which results in a new juvenile form of these species or which results in the adult is not appropriate for association with items of the 29-- series, but should be coded only as reproduction with a symbol of the A--- series.

17. Symbol series 3---; coding of genetic changes which can be caused or affected or prevented by the test compound

Aberrations of the genetic structures are coded by symbols of series 3---. Many of these are known to have a given incidence without influence of chemicals or any other specific agent. The test compound's effect in causing or preventing the genetic change is indicated in Field T-1 with Symbol 7 or 3, respectively. (Symbols 3, 31, 311, 312, 3121, 3122, 3123, 3124, 3125, and 34 all are coded only with Symbol 7 or 3 [or 8, 9, A, or C], never with Symbol 1 or 2 of Field T-1.) Symbols of the 312- series should not be used to code incidence of translocation, incidence of inversion, incidence of gene mutation, etc., as well as to code the process; this is the reason Symbols 1 and 2 of Field T-1 are not used with these symbols of Field T-2. The series could be expanded to include symbols specifically for incidence of gene mutation, incidence of deletion, etc., (i.e., incidence of aberrations of symbol series 31--) or for incidence of anatomical or physiological aberration coded by symbols of

series 32-- and 35--. The only suitable item now in the Field T-2 3--- series is Symbol 33, rate of unspecified genetic change, with which Symbol 1 or 2 of Field T-2 is used.

Symbol 34 is used to code aberrations of the genetic structures of cells other than germinal cells. In higher animals, such a mutation would not be inheritable nor, in the adult animal with its finally matured tissues, would the mutation most frequently be detectable; in plants and the more simple animals, however, a somatic mutation may be inherited by the mutated part reproducing either sexually or asexually and whatever vegetative or somatic tissues and organs are produced by the mutated cells will reveal any anatomical or physiological changes due to the mutation. Therefore, the coding of "somatic mutation" does not represent a code classification of mutations that are not inheritable by having occurred in cells other than germinal cells.

Symbols of series 32-- and 35-- (of which, to date, there are only the two general items, Symbols 32 and 35) are for coding the anatomical or physiological changes in the organism which are brought about by the modification of chromosome structure of the cells (whether it is germinal or somatic mutation). In each of these series may be placed a limited number of items representing specific anatomical and physiological deviation due to chromosomal modification. Symbols 7 (causes) and 3 (prevents) are the only symbols of Field T-1 to be used with symbols of the 32-- and 35-- series; the normal incidence of such an anatomical or physiological deviation would be given a symbol of the 33-- series and a test compound's effect on that incidence would be coded with Symbol 1 or 2 in Field T-1.

The use of Symbol 32 and the use of Symbols 511 and 521 (adaptations which are "genetic" in that the adaptations occur gradually with succeeding generations) are sometimes confusing. All of the items of symbol series 5--- are concerned with the test organism's adapting to the test compound (e.g., the test organism's becoming tolerant of or resistant to the test compound). A symbol of the 5--- series codes the adaptive effect, without pretending to distinguish as to whether it is due to a chromosomal mutation. In the case of Symbols 511 and 521, the symbols indicate only that a tolerance or sensitivity (511, with Symbol 1 or 2 in Field T-1) or increased virulence or attenuation (521, with Symbol 1 or 2 in Field T-1) were produced over several generations and there is no evidence as to whether it is the result of selectivity or actual genetic mutation. If it were demonstrated to be genetic mutation, the adaptation should not be coded with Symbol 511 or 521, but should be coded with a special symbol added to the 35-- series.

18. Symbols 4165 and 4166; coding of chlorosis (deficiency of chlorophyll) and abnormal depth of color (presumably abnormally large quantity of chlorophyll) due to, or affected by, the test compound or secondary compound

The coding of the deficiency of chlorophyll has been a problem partly because of its nature, chlorosis being generally a symptom of one or another deficiency disease. Although it is possible to do it by use of Symbols F824, FA24, FI24, and FE-- (coding in Field D chlorophyll as the specific compound whose synthesis, deposit, withdrawal, or destruction is affected), so much general screening data on chlorosis was encountered that it seemed more practical and adequate to provide a special symbol for the pathological condition, for sake of simplicity. The condition has been associated somewhat inappropriately with discolorations (e.g., russeting of fruits), though it actually does not classify any more suitably elsewhere in Field T-2; thus, its symbol is 4165. An associated condition, which has been described as a result of certain test compounds, abnormal depth of color (due presumably to an excess of chlorophyll), has been assigned Symbol 4166. It is by these two symbols that the CBCC codes all production of (and effects on) these two conditions by the test compound or secondary compound.

19. Symbols 43, 44, 45, 46, and 47; carcinogen-induced tumors; coding of their production and coding of their treatment by the test compound or secondary compound

As indicated by the definition of Symbol 43, the production of a tumor by the test compound is coded only by Symbol 43. When a tumor has been induced by a chemical or is spontaneous and is SUBSEQUENTLY treated by the test compound (i.e., treated by a chemical other than the one that induced the tumor), only Symbol 44, 45, 46, or 47 may be used and the fact that the tumor was induced or was spontaneous is coded in Field F by Symbol T or U.

In the situation in which the test compound is administered with a second compound whose carcinogenic ability when administered alone has been demonstrated, in order to determine the test compound's effect on the carcinogenic ability of the second compound, no tumor exists at the time of administration. The action of the test compound is not on a tumor, therefore, but is on the candidate carcinogenic action of the secondary compound, Field T-1 is coded with Symbol 8, 9, or C, and Field T-2 is coded with Symbol 43.

20. Symbols of the 51-- series; tolerance

General use of Symbols 51, 511, 512, and 513 vs. Symbols 514 and 5131; 51-- series vs. Symbol 58:

Symbols 51, 511, 512, and 513 are used to code the phenomenon whereby the test organism develops a tolerance to the test compound through administration (usually repeated administration) of the test compound. This is discussed in the Key in Fields M and N (Division 11 of Specific Directions and Explanations for Fields M and N). The original specific chemical effect (diminishing with any tolerance development) is coded in Field T-1 and T-2 by another code line. (See the Specific Directions and Explanations for Field G, Division 11.) The basic distinctions between the definitions for Symbols 51, 511, 512, and 513 are made in the Code. The test compound's "action" (the development of tolerance) is coded in Field T-1 as an increase over the level of tolerance existing at first exposure to the test compound (Symbol 1 of Field T-1). Symbol 2 of Field T-1 is used with Symbols 51, 511, 512, and 513 to indicate a decrease of tolerance (i.e., to code a production of [increase of] sensitivity). With these Field T-2 symbols, Symbol 8, 9, A, or C is used in Field T-1 to code the test compound's effect on the increase or decrease of tolerance to a secondary compound due to administration of the secondary compound. To code an increase or decrease of tolerance to a secondary compound due to administration of the test compound, use Symbol 514 or 5131. "Sensitization" is defined as a specific phenomenon distinct from increase of sensitivity and is coded by Symbol 58.

Symbol 511:

Symbol 511 is used for coding the production of a tolerant race of the test organism (tolerant to the test compound) due to exposure to the test compound. (This does not necessarily imply either genetic mutation by the test compound nor the survival of naturally occurring tolerant individuals; it implies only that exposure to the test compound results in tolerant individuals whose tolerance to the test compound is inheritable.) Only Symbol 1 in Field T-1 is used to code the increase in inheritable tolerance. Use Symbol 2 in Field T-1 to code the decrease in inheritable tolerance (i.e., the production of a race with increased sensitivity). Use Symbol 8, 9, A, or C in Field T-1 to code the test compound's effect on the increase or decrease of inheritable tolerance to a secondary compound due to exposure to the secondary compound. To code an increase or decrease of an individual's tolerance of a secondary compound due to administration of the test compound, use Symbol 514 or 5131.

Symbols 513 and 5131:

Symbol 513 is used for coding the increase in tolerance to the test compound due to administration (usually repeated) of the test compound at a dosage level considerably below the level producing the effect for which tolerance is developed. Use only Symbol 1 in Field T-1 with Symbol 513, since the term tachyphylaxis is used to imply increase in tolerance and never a decrease. Use Symbol 8, 9, A, or C to code the effect of the test compound on the increase of tolerance to a secondary compound due to tachyphylactic administration of the secondary compound. To code the increase in tolerance to a secondary compound due to tachyphylactic administration of the test compound, use Symbol 5131.

Symbol 514:

Use only Symbol 1 of Field T-1 to code the increase in tolerance to the secondary compound. (Symbol 514 is limited to use for coding "cross-tolerance" and therefore is not used with Symbol 2 in Field T-1.) Use Symbol 8, 9, A, or C to code the test compound's effect on the increase in tolerance to a third compound caused by administration of a secondary compound (the third compound can only be written in Field D).

21. Symbols of the 5C- series; resistance of the host to a pathogen, tumor, or non-infectious pathology

Reference to symbols of the 51-- series will reveal that they code the development of tolerance for (resistance to) the test compound or a secondary compound, by the organism to which administration was made.

Resistance (tolerance, refractoriness, lack of sensitivity) can also be developed to specific pathological organisms and the concept can be extended to tumors and non-infectious diseases. Possibly this resistance to pathology is actually always a chemical phenomenon in the final analysis, but the specific chemical stimulant of antibody production is unidentified except by the name of the associated pathology.

One possible use for symbols of the 5C-- series would occur when an extract (vaccine) had been prepared from the pathogen and injected. Such an extract might be given a CBCC chemical serial number (a series of natural preparations of unspecified chemical nature have been given CBCC chemical serial numbers). While the effect of such vaccines (as test compounds) would probably never be selected for coding by the CBCC (Symbol 5C with Symbol 7 in Field T-1), the effect of a test compound on the vaccine (coded in Field D as a secondary compound) might be selected for coding. A test compound might conceivably affect actively acquired resistance due to exposure to the pathology or affect natural resistance to the pathology. It is not impossible, however, that specific compounds with known structure might be tested specifically for their ability to induce resistance to tumors, pathogens, or non-infectious pathologies (Symbol 5C with Symbol 7 in Field T-1).

22. Symbols of series 7---; coding of effects of test compounds on the actions of enzymes; omission of coding the altered substrate, when an enzyme is identified in Field T-2; the Enzyme Code of Field T-2

Enzymes act as catalysts in biological organisms (biological systems) in regulating metabolic activities. When a test compound affects, or is tested to affect, the normal activity of an enzyme, the enzyme is essentially the secondary compound of the situation. However, the CBCC coding procedure has treated enzymes in a way quite different from the usual treatment afforded secondary compounds. The usual procedure involves coding any secondary compound in Field D and, in Field T-2, the biological process affected by the secondary compound. However, in the case of the activity of any enzyme, the enzyme is not identified in Field D, but in Field T-2.

By using Field T-2 to indicate the identity of a specific enzyme, there remains no field to code the specific process affected by or caused by the enzyme. This, however, is not considered to be a serious problem in the case of enzymes. The enzyme nomenclature is built on the functional aspect. (Examine the Enzyme Code, appended at the end of the Field T-2 symbols, following the F--- series.) Thus, the enzyme itself indicates the metabolic process.

Attention is called to the items of Field T-2 defined as chemical alteration and coded by symbols of series FE--. When a test compound affects the alteration of a secondary compound in the biological organism, the alteration is coded by the appropriate symbol of the FE-- series (with Symbol *, the IBM 12 zone punch, in Column 61) and the compound altered is coded in Field D. Actually, such an alteration which the test compound affects is brought about or controlled by a metabolic enzyme and the effect of the test compound is ordinarily an effect on that enzyme or enzyme system. The CBCC does not translate the alteration into terms of a general enzyme and code Field T-2 with such an enzyme type; instead, it codes only the alteration. Only when the author indicates that the test has actually demonstrated specifically that the action of a given enzyme (named by the author) has been affected does the CBCC code Field T-2 with the enzyme.

If any disadvantage exists in the pattern whereby Field T-2 is used to code an enzyme rather than the process caused by the enzyme, it is that, in retrieval of information on an alteration of any of certain secondary compounds (any of the substrates which an enzyme might affect) affected by the test compound, the search in Field T-2 must include not only the symbol for the specific alteration (one of the FE-- series), but also all the enzymes (of the 7--- series) known to cause that alteration. While this has not proved an inconvenience of serious proportions to the CBCC, it is suggested that a preferred procedure might involve coding in Field T-2 the alteration in any case (even when the enzyme is named by the author as being affected in its catalytic alteration of a biological compound), coding the secondary compound altered (i.e., the substrate altered by the enzyme) in Field D, and devising a new coding field for coding the identity of the enzyme involved.

When Field T-2 is coded with an enzyme (a symbol of the 7--- series), the chemical altered by the enzyme is not coded in Field D. (See the last paragraph of Division 7, Specific Directions and Explanations of Field D.) This CBCC rule was devised because, as pointed out above, the chemical

altered is implicit in the name of the enzyme. From the standpoint of retrieval of information, this may represent a disadvantage, however, since in programming retrieval of information on any given biological compound (or biological compound type), if the plan included a search for the compound treated as a secondary compound (Field D), Field T-2 must be searched for enzymes known to affect that particular biological compound. Thus, it is suggested that it might be more advantageous, in another coding program, always to code Field D with the compound altered in spite of the fact that the coding of Field T-2 adequately implies the identity of the altered compound.

The coding of Field T-1, when Field T-2 is coded with an enzyme, is according to the following pattern:

When the test compound inhibits the enzyme, use Symbol 2 or 3.
When the test compound stimulates (potentiates) the enzyme, use Symbol 1.
When the test compound is a coenzyme to the enzyme, use Symbol 7.
When the test compound affects the action of a secondary compound on the enzyme, use Symbol 8, 9, A, or C.

Information about the effect of an enzyme on the test compound is not coded by the CBCC, when the effect is expressed by naming the enzyme and when the enzyme is coded in Field T-2. Effects on test compounds are coded only by symbols of series FE-- when the specific alteration is named. This is discussed in Division 26.

Information about the effect of the test compound on the enzyme (rather than on the action of the enzyme), such as the amount, synthesis, or destruction of the enzyme, is not coded.

When the test compound has an effect on metabolism through its effect on any enzyme, the enzyme should be coded in Field T-2 rather than to translate the enzyme action into one of the metabolism symbols of the Field T-2 F--- symbol series.

When the effect of a test compound on an enzyme is coded, the organism source of the enzyme should be coded in Field E, the organ or tissue source should be coded in Fields H-1 and/or I, and Field G-1 should indicate the state of the organ or tissue source (e.g., extract or slice of the tissue, Symbol V or X of Field G-1).

Appended to the Taxonomy Code of Field E are three special items, to be used only for indicating general sources of enzymes when the specific organism source is unknown or is not specified by the author. These are Symbols Z, Z1, and Z2.

The section of Field T-2 which lists specific enzymes with their code symbols is designated as the Enzyme Code. These Field T-2 code symbols do not represent CBCC chemical serial numbers nor do they reveal the structure of the enzyme; they are special symbols conforming to the pattern of Field T-2, having four units. The first unit (7) identifies the item as being an enzyme, the second (Column 59) indicates the general type of enzyme, the third (Column 60) specifies either a sub-type or a specific enzyme of the type indicated by the second unit, and the fourth and final unit (Column 61) indicates a specific enzyme of a sub-type specified by the third unit. Since enzymes are named for the substrate whose alteration they catalyze, the symbols reflect this information by their structures.

It was intended that the enzyme list be revised at frequent intervals or continually, to keep it up-to-date. Circumstances have not permitted this. The last revision was in 1953; the following is quoted from the introduction prepared by Dr. I. D. Welt for that edition:

> "The classification of enzymes is difficult because of the relative non-specificity of some of these substances and also because of the lack of agreement among enzymologists. It is possible in some codes at least to assign a given enzyme to more than one category, and a classified listing such as the one presented must be regarded as tentative and subject to revision when more becomes known about the intimate details of the reactions which are catalyzed. In the indexing of enzymes, certain broad groups have been selected as a suitable arbitrary pattern for classification.

"... it has been decided not to delete symbols of enzymes which may be later shown to consist of more than one entity. Instead, cross-references will be used to cope with this situation.

"All possible attempts have been made to include all enzymes known as of July 1953. The following books have been found very helpful:

1. The Enzymes. Chemistry and Mechanism of Action. Edited by James B. Sumner and Karl Myrbäck.

   Vol. I, Part 1 (1950)
   Vol. I, Part 2 (1951)
   Vol. II, Part 1 (1951)
   Vol. II, Part 2 (1952). Academic Press, N.Y.C.

2. Chemistry and Methods of Enzymes. 3rd Edition. By James B. Sumner and G. Fred Somers. Academic Press, N.Y.C. (1953)."

Since this 1953 revision, so many enzymes have been described that the list presented here may be regarded as obsolete, although, had revision been possible to bring it up-to-date, another five years would doubtless find it in the same state of obsolescence. While this fault is recognized, it is not unique to the enzyme list; the Taxonomy Code of Field T-2 will be found inaccurate and to become more so as time passes for the same reasons of advances in knowledge of organisms' taxonomic relationships. In spite of this, the Enzyme Code is included, just as is the Taxonomy Code, to illustrate the method whereby the CBCC has assigned symbols, to provide a reference to the CBCC files of coded data, and to serve as basis for a future corrected and expanded list. A recent valuable listing and description of enzymes which should be consulted in revision of this list or in building a new Enzyme Code is ENZYMES by Malcolm Dixon and C. E. Webb, Academic Press, N.Y.C., 1958.

The Enzyme Code, as used by the CBCC, is in two forms, one arranged as it is here, according to the natural organization (and therefore according to the heirarchy of symbol structure), the second arranged alphabetically by name. While both have been useful, the alphabetical list must be considered a supplemental list because like the alphabetical list of other Field T-2 items prepared for CBCC use, its use leads to incorrect selection of code symbols in coding data, due to not being able to scan all related items listed together and to make the most appropriate selection.

23. Symbol 8153; extension of the invertebrate body from its encasement or shell

This condition was added to Field T-2 when coding a large collection of data from molluscacide tests in which one of the typical toxic responses was described merely as the body of the snail being extended from the shell and apparently incapable of withdrawal into the shell. The definite cause for this is not determined and may in some cases be due merely to osmotic phenomena resulting in tissue swelling, though this was not indicated by the description of the response. The phenomenon has been arbitrarily assigned Symbol 8153, associating it with muscular conditions, rather than to code all the data involved as being merely an unspecified systemic toxicity. The term and symbol are candidate for revision with more specific information about the condition.

24. Symbols of series 821-; blood pressure

The definitions of Symbols 821, 8211, and 8212 indicate their use and limitations. The maintenance of a blood pressure that is normal for any given individual is the result of a regulated balance of a number of factors. Symbol 821 can be regarded as representing this balance itself and if all that is known about the test compound's effect is the disturbance of the balance, without indication as to whether the pressure is generally increased or decreased, Symbol 821 can be used with Symbol 6 of Field T-1; since such data are improbable and, even if existent, would probably be rejected for coding by the CBCC, Symbol 821 is virtually nothing but the heading for the 821- series.

Symbols 8211 and 8212 code blood pressure disturbances due only to vasomotor effects (vasopressor and vasodepressor). For an increase (or a decrease) in blood pressure due to any other mechanism or factor, a new symbol or symbols must be added to the Code. For example, none of the following specific states of blood pressure have yet been entered in Field T-2 and assigned a symbol,

even though the factors themselves, such as abnormal blood volume, vasodilation, vasoconstriction, sclerosis, etc., do have Field T-2 symbols: blood pressure increase due to increased blood volume, decreased pressure due to decreased blood volume, pressure changes known to be due to direct action on vessel musculature (vasodilation, vasoconstriction) rather than due to indirect action on vessel musculature (vasomotor action, Symbols 8211 and 8212), pressure increase due to loss of elasticity of vascular walls, etc.

25. Symbols F6--, F8--, F9--, FA--, FB--, FC--, FG--, FH--, and FI--

General explanation has been made in the Code for the use of these symbols, but it has not been convenient to include with their definitions in the Code all the instructions and explanations important to understanding their use. For each symbol, these additional comments are included here:

Nutrient uptake

F6--: Use Symbol F6-- only to code the physiological process (uptake of nutrients) at the cellular level of the organism. For the process of feeding or ingestion, use Symbol F3. Symbol F6-- is used also for the process of a plant's taking materials from the soil, water, or other medium in which it is growing, as well as for the uptake of these materials (and the plant's distributed photosynthetic products) by the plant's tissues. Since test compounds are not considered to be nutrients, Symbol F6-- will not be combined with Symbol B to form the composite Symbol F6B.

Chemosynthesis

F8--: Since the CBCC does not code information about normal metabolism, the organism's ability to synthesize the test compound would not be coded, unless Field E is coded with a pathology one of the symptoms of which is the abnormal synthesis of the test compound. Only under this situation can Symbol F8-- be combined with Symbol --B to form the composite Symbol F8B. Symbol F8-- is to be used for coding production of the compound; although it is defined in terms of synthesis, the symbol can be used whether the compound is formed by the organism through actual synthesis or as the result of a breakdown of a larger molecule.

Distribution

F9--: Use Symbol F9-- for translocation and migration of nutrilites and metabolites from the sites of origin or storage. Code in Field H-1 the site from which distribution is made, unless the distributed material is fed, injected, or otherwise administered, when the site of administration need not be coded in Field H-1. Distribution of the test compound is not to be coded (except in the case of its being concentrated or stored, which is coded by use of Symbol FA--) and therefore Symbol F9-- can not be combined with Symbol --B to make the composite Symbol F9B.

Storage, deposit

FA--: Code in Fields H-1 and/or I the site of storage or deposit. Do not use Symbol FA-- with Symbol 2 of Field T-1 to indicate withdrawal of material from a given site, but use Symbol 2 only to code a decrease (from normal) of the rate of deposit or a decrease (from normal) of the total quantity; to code a withdrawal, use only Symbol FI--. Symbol FA-- can be combined with Symbol --B to make the composite symbol FAB with which only Symbol 7 can be used in Field T-1.

Absorption

FB--: Code in Fields H-1 and/or I the site of absorption. Use Symbol FB-- for the selective resorption into the blood of materials from the renal tubule. (For the general process of filtering the blood at the renal corpuscle, use Symbol 87B1. For the general renal process resulting in excretion of a specific material in the urine, use Symbol FC-- or FF1-.)

Excretion, secretion, etc., of the normal secondary compound

FC--: For Symbol FC--, the term "normal" is used to describe (1) any specific chemical normally a component of the organism as a whole, (2) any specific chemical normally consumed or absorbed by the organism and contributing beneficially to its normal activities, or (3) any specific chemical normally a metabolic product of the organism. This normal material may be thrown off through excretory or exocrine secretory organs unaltered by those organs or it may be chemically altered by the organs before being discharged as a normal component of the organ's product. Thus, loss or discard of any material is coded by Symbols FC-- and FF--, the distinction being that Symbol FF-- denotes the discard of material FOREIGN to the excretory path (or exocrine path), while Symbol FC-- denotes discard of materials NORMAL to the path. (See also Division 27.) Symbol FC--, like Symbol FF--, is intended only for test compound effects on LOSS or DISCARD of materials. In particular, the symbol is not intended for test compound effects on endocrine secretory activities producing specific chemical products normally used internally for regulatory purposes, for which Symbol FE (with an asterisk in Column 61) or F85- would be used, with the secretory organ coded in Field H-1. However, for test compound effects on any discard of normal hormones through normal paths, use Symbol FC5- with the excretory organ or exocrine gland in Field H-1 and the specific hormone in Field D. (For effects on discard of hormones foreign to the organism or of the organism's own hormones over abnormal paths, use Symbol FF-5.) If any material being discarded is a normal material chemically altered or a normal product produced by chemical alteration and if the test compound effect is precisely on the chemical alteration by the excretory organ or exocrine gland, use Symbol F8-- or FE--, instead of Symbol FC--. Code in Fields H-1 and/or I the excretory organ or tissue or exocrine gland. Since Symbol FC-- is used only for discard of normal materials, it can not be combined with Symbol --B to make the composite Symbol FCB. Only Symbols 1, 2, 3, 8, 9, A, or C of Field T-1 may be used with Symbol FC--. Symbol FC (with no coding in Column 60 or 61) can be used to code the general normal excretory or secretory function (of an organ or tissue in Fields H-1 and/or I, through which normal materials are discarded) which function can be affected by the test compound.

Ability to permeate or penetrate

FG--: Use Symbol FG-- when the ability of the specific secondary compound to permeate or penetrate is affected by the test compound. When the test compound effect is on the membrane, altering its character rather than the penetrating ability of the secondary compound, use Symbol 842. Symbol --B cannot be combined with Symbol FG-- to make the composite Symbol FGB, since the test compound can not cause or affect its own ability to penetrate or permeate; the test compound's ability to penetrate or permeate is equivalent to its capacity for being absorbed and is coded by Symbol FBB.

Incorporation of the test compound

FH--: Use Symbol FH-- to code the test compound per se being incorporated into the structure of a compound synthesized by the test organism (the test compound ordinarily being a labelled compound or element, detectable after its being used by the organism in chemosynthesis). In coding this effect on the test compound, only Symbol 7 is used in Field T-1, just as in the case of coding specific chemical alterations with symbols of the FE-- series. To code the test compound's influence on the similar incorporation of a secondary compound into one of the organism's constituents, use Symbol 8, 9, A, or C of Field T-1 and code the secondary compound in Field D (writing in Field T-2 the specific identity of the compound which is coded only as to type in Field T-2). This is a more specific coding than to indicate only that the test compound can substitute (Symbol A of Field T-1) for the material normally used for synthesis of the compound (Symbol F42- of Field T-2). Note that Symbol --B would never be combined with Symbol FH-- to make the composite Symbol FHB. This is because the stipulation of the test compound is made by Symbol FH-- itself when used with Symbol 7 of Field T-1; appending Symbol --B to it would be erroneous (i.e., the statement, "the test compound is incorporated into the test compound", is meaningless).

Withdrawal of the secondary compound (or test compound)

FI--: Code in Fields H-1 and/or I the site of withdrawal. (Use Symbol FA-- to code deposit or storage of a compound.) Use Symbol 7, 1, 2, or 3 (or 8, 9, A, or C) of Field T-1 with Symbol FI-- to code the test compound's causing withdrawal or speeding or slowing a normal withdrawal or a withdrawal caused or affected by secondary compounds. Since the stored or concentrated test compound would not itself cause its withdrawal, nor would administration of more of the test compound be apt to cause the withdrawal from a deposit of the test compound, Symbol FI-- is not to be combined with Symbol --B to make the composite Symbol FIB, except when Field E is coded with a pathology, one of whose symptoms is the withdrawal of the test compound from a site of normal deposit. This effect on the test compound by pathology can be coded as justifiably as can be coded the alteration of the test compound by the normal organism.

26. Symbols of the FE-- series; alteration of the test compound, secondary compound, or third compound

Symbols of the FE-- series are unique in that they do not represent biological states or processes which the test compound can cause or affect, but, on the contrary, represent an effect on the test compound (or a secondary compound or a third compound) by the test organism. (Of the other symbols of Field T-2, only Symbols F8B, FAB, FBB, FH--, and FIB fall within this definition.) In the case of the FE-- series, the effect is chemical alteration by the normal test organism or a pathology coded in Field E.

With symbols of the FE-- series, the coding of Fields T-1, T-2, and D is according to the following pattern:

(A) Alteration of the test compound: Only Field T-1 Symbol 7 can be used, being interpreted under these conditions as "undergoes" (e.g., "the test compound undergoes oxidation"). The specific alteration is coded in Field T-2 and the by-product, if known, is coded in Field D.

(B) Effect of the test compound on alteration of a secondary compound: Field T-1 Symbol 1, 2, or 3 can be used; also, Field T-1 Symbol 7 can be used to indicate a test compound's being essential for the alteration of the secondary compound. The secondary compound's specific alteration which is affected by the test compound is coded in Field T-2 and, in addition, Symbol * is placed in Column 61. The secondary compound whose alteration is affected is coded in Field D. The by-product of the secondary compound's alteration is written, not coded, in Field T-2.

(C) Effect of the test compound on a secondary compound's effect on the alteration of a third compound: Only Field T-1 Symbol 8, 9, A, or C can be used. The third compound's specific alteration which is affected by the secondary compound is coded in Field T-2 and, in addition, Symbol * is placed in Column 61. The secondary compound antagonized, synergized, simulated, or whose action is additive with the test compound, is coded in Field D. The identities of (1) the third compound whose alteration is affected by the secondary compound and (2) the by-product of the third compound's alteration are written, not coded, in Field T-2.

Fields H-1 and I are always used to code organs or tissues affected by the test compound. However, when a compound's alteration by the test organism is coded (symbols of the FE-- series), Fields H-1 and I are coded to conform to this particular type of information. Under this situation, then, Fields H-1 and I should be coded only with the site of alteration, if known (i.e., with the organ or tissue of the organism causing the compound's alteration).

When an alteration of the test compound is demonstrated to be caused by an enzyme, the information is never coded by the CBCC. The ruling evolved, because the CBCC procedure for coding information from studies on specific enzymes involves identifying the specific enzyme in Field T-2, by coding there its specific symbol from the Enzyme Code. In doing this, the specific typical action of the enzyme is indicated by the name of the enzyme. (Consult Division 22 and the Enzyme Code.) When using Field T-2 in this way for coding enzymes, the use of Field T-1 has been patterned so that none

of the available Field T-1 symbols can be used to indicate that the action of the enzyme in Field T-2 represents the alteration of the test compound. The original philosophy may be supposed to have been that a provision for coding the fact that a specific enzyme brought about a test compound's alteration was unnecessary, because it is not the intent of the CBCC to code in vitro actions of one compound (the enzyme) on another (the test compound); even though enzymes represent products (or even might be considered as components) of living organisms, the fact that the demonstration of the enzyme action on the test compound is nearly always in vitro contributed to the concept that the test compound's alteration should not be coded, because the results can not necessarily be inferred to occur in the living organism (i. e., the alteration of the test compound by the enzyme in vitro can not be assumed to be an alteration of which the test organism [source of the enzyme] is capable by its enzyme in vivo). In connection with this, it should be understood that the coding of alterations of test compounds (and secondary and tertiary compounds) has been a more recent development in the CBCC Code; the information was not selected for coding during the first years. This represents another factor contributing to the establishment of the ruling not to code the test compound's alterations by specific, named enzymes.

It is suggested, however, that this ruling be revised so that information on alteration of the test compound by specific enzymes be coded when the enzyme is named. Without altering the procedure to be used when the enzyme is coded in Field T-2 (i. e., when the test compound affects a specific enzyme), the enzyme action could be translated into one of the alterations designated by a symbol of the FE-- series and the alteration coded accordingly. It would not seem necessary, if this procedure were adopted, to make any special coding provision for indicating that it was an in vitro demonstration, since this is generally the case with most demonstrations of alteration of the test compound as well as of effects of the test compound on enzyme actions.

When the test compound is demonstrated to affect a specific enzyme's alteration of a secondary compound, the CBCC does not code Field T-2 with the alteration affected (a symbol of the FE-- series), but always codes Field T-2 with the specific enzyme, coding Field T-1 as indicated in Division 22 and coding the secondary compound in Field D.

Occasionally, information is encountered which describes a chemical as having been demonstrated to be used by a biological system as the precursor for a specific chemical component or product of the organism. This does not mean that it is incorporated per se into the final product and therefore it should not be coded by use of Symbol FH--. Further, the fact that the test compound is actually altered to another specified material does not make the process suitable for inclusion with those symbols making up a series describing the metabolic fates of unaltered compounds (Symbols FG--, F8--, F9--, FA--, FB--, FC--, FG--, FH--, and FI--), but more logically associated with symbol series FE-- specifically concerned with alteration. The chemical reactions which involve this use of the precursor to synthesize the final product are seldom described or known; therefore, specific symbols of the FE-- series can most frequently not be used to describe the specific alteration of the precursor. The CBCC has, however, coded such information simply by indicating that the test compound is altered (using Symbol FE in Field T-2, with no coding in Column 60 or 61) to the product coded in Field D.

In Column 61, letters A through I have not been used in making symbols for the FE-- series because, with this series, the IBM 12 zone punch (Symbol *) has been assigned to the purpose explained above.

27. Symbols of the series FF--; excretion, secretion, etc. (elimination) of the test compound; elimination of materials foreign to the test organism or foreign to a specific path of elimination which can be affected by the test compound

When Field T-2 is coded to describe the process of excretion, secretion, or vomiting of the test compound (Symbol FF-B), only Symbol 7 of Field T-1 can be used. When Field T-2 is coded to describe excretion, secretion, or vomiting of any foreign material other than the test compound, Field T-1 can be coded to indicate the test compound's increasing, decreasing, or preventing (Symbol 1, 2, or 3), being essential for (Symbol 7), antagonizing, synergizing, simulating, or being additive with a secondary compound's effect on (Symbol 8, 9, A, or C) the secretion, excretion, or vomiting of the foreign material.

When using Symbol 8, 9, A, or C in Field T-1, Field D must be coded with the compound antagonized, synergized, simulated, or whose action is additive with the test compound; under these

circumstances, the foreign material excreted, secreted, or vomited, if its specific identity is known, is written, not coded, in Field T-2.

28. Use of symbols of series FC-- compared to use of symbols of series FF--; coding of general functions of excretory and exocrine secretory structures

The processes of excretion and secretion do not lend themselves easily to being classified separately; many "excretory" organs are quite legitimately regarded as secretory and many "secretory" organs certainly serve as paths for excretion. Excretion and exocrine secretion are treated together in this Code, for purposes of coding the processes of an organism's discard or loss of chemical materials. (Endocrine secretion is not included in the category of metabolic activities dealing with discard and loss.) Instead of attempting to distinguish between excretion and exocrine secretion, the Code distinguishes between (1) normal discard and loss which a test compound (or secondary compound) can effect (FC--) and (2) the test compound's discard or loss (FF-B); the second of these two categories (which represents discard or loss of a foreign material, the test compound) is expanded in definition to provide symbols for coding the discard or loss of any foreign material (FF-1 through FF-L).

Effects of test compounds on the processes of discard or loss from the organism are most frequently in terms of an effect on the loss of a specific material or a specific type of material, whether it is normal or foreign. Thus, the test compound may be described as decreasing, increasing, or stopping discard or loss of a carbohydrate, a protein, a hormone, etc. It is for this effect on metabolic loss of specific materials that symbols of series FC-- are ordinarily used and for which symbols of the FF-- series (except FF-B) are invariably used. However, a test compound's effect can be in terms of merely an effect on the general activity of an excretory or exocrine secretory organ or tissue, without indicating that any one of the many specific materials the organ or tissue may normally secrete or excrete is specifically affected. To code this effect of the test compound, symbols of the FF-- series should never be used, but only FC (with nothing coded in Columns 60 and 61), coding the specific excretory organ or exocrine gland or glandular tissue in Fields H-1 and/or I. This latter coding in Field T-2 is preferred over using Symbol 15, since it is more specific.

29. Symbols available for expansion of Field T-2

Examination of the Code will reveal that an enormous number of symbols remain available for new biological conditions, qualities, or processes which can be caused or affected by test compounds or secondary compounds. This is true not only for new series (Symbols E through Z in Column 58), but within series (Columns 59 through 61), since in none of the series have the items been so numerous that all symbols of any one column have been exhausted through Symbol Z. Only one restriction exists which was pointed out earlier. With symbols of the FE-- series, Symbols A through I can not be used in Column 61, since Symbol * (the IBM 12 zone punch) is used in that column for a special purpose with that series of symbols.

30. File of coded biology data arranged by biological state, quality, or process

The CBCC maintains a file of its coded biology data on IBM punched cards arranged according to entries in Field T-2 so that information about any specific biological state, quality, or process that can be caused or affected by test compounds (or information about any specific alteration of test compounds) can be retrieved manually. This is because so much retrieval of coded information is begun most efficiently by sorting for these particular entries.

31. Double coding in Field T-2

Field T-2 is never to have more than a single entry in any one code line, except that Symbol * may be coded with symbols of the FE-- series in Column 61 as explained in Division 26. When Symbol * is coded in Column 61 (representing essentially the coding of two categories of information, rather than double coding), both it (the 12 zone punch) and the numerical or letter symbol accompanying it in the column are punched on the same IBM card in that column; a second card is not punched with the 12 zone punch omitted. In the IBM Punched Card File arranged according to entries in Field T-2, the card is filed in the sequence indicated by the code symbol for the secondary or a third chemical's alteration.

CATEGORY OF THE TEST COMPOUND'S EFFECT REPRESENTING PRACTICAL USE

Organization

Field T-3 symbols have three units. Because IBM sorting is more direct when only numbers are used as units of symbols, letters have so far not been used in Field T-3 symbols.

The items of Field T-3 are arranged by only three categories (i. e., symbol series 1--, 2--, 3--), as defined and explained in the section on Specific Directions and Explanations.

General Use

In Field T-3, the chemical effect coded in Fields T-1 and T-2 is described in terms of one of certain broad categories of effects. Examples of these are (1) curariform effect: all specific responses which are likewise caused by curare, Symbol 229; (2) parasympathomimetic: all specific responses which are likewise caused by stimulation of the parasympathetic nervous system, Symbol 226; (3) rodenticide: death caused to any species of rodent, Symbol 115; and (4) mydriatic action: contraction of the radial muscles or relaxing of circular muscles of the iris, Symbol 222.

The Field T-3 categories of test compound effects are defined to refer to a practical use. For example, the CBCC uses the terms of Field T-3 to separate, from all information on lethal effects, that information relating to practical use in population control of organisms. If information is wanted on all lethal effects on any group of organisms or of any group of test compounds, sorting should never be in Field T-3, but only in Field T-2, whereas, if information is wanted on compounds which might be considered specifically as herbicides, rodenticides, bactericides, etc., retrieval should be only by Field T-3. This distinction from coding in Field T-2 is made by all terms of Field T-3.

One difficulty in classifying chemical effects by symbols of Field T-3 is that of interpretation of the test results in coding the information. For example, although the literal meanings of herbicide or rodenticide may be merely the killing of plants or killing of rodents, the categories indicated by Symbols 108 and 115 of Field T-3 refer to practical control of plant or rodent populations, as explained above. Thus, when a test compound is administered by injection in a rodent or a plant and death results, the death by injection can hardly be considered as a practical method for control of the rodent or plant and Field T-3 should not be coded with Symbol 108 or 115 to suggest that the test has demonstrated practicality for those purposes. Coders have always found very difficult understanding that lethal effects should be coded by the terms of Field T-3 describing killing only when the method of testing represents a practical control method, whereas Field T-1 and T-2 should be coded with all lethal effects, whether or not caused by a method that might be practical for population control.

A major difficulty in use of Field T-3 items is that of interpreting consistently and accurately all specific physiological effects (coded in Fields T-1 and T-2) in terms of the general type of pharmacological effect of Field T-3. In the literature, an author commonly considers it unnecessary to point out to his specialized reader that a specific response is actually adrenaline-like or sympathomimetic, for example. Even coders with considerable pharmacological training who, on reflection, would recognize a specific effect as being adrenaline-like or sympathomimetic are apt to neglect doing so; in the case of coders not familiar with all aspects of sympathomimetic action, the coding problem is even more acute.

Specific Directions and Explanations

1. Symbols of the 1-- series; effects connected with control of populations of the test organism; death, attraction, or repulsion as an objective in control of organism populations

Most of the symbols of the first series of Field T-3 are used to indicate that a lethal effect is the effect desired and represents the use for which the compound is tested. Since this is not true of all lethal effects of test compounds on the test organism, Field T-3 serves to classify death produced

by test compounds into two categories, an undesired effect (when a non-toxic compound is wanted for purposes such as therapy) and an intended effect (when a toxic compound is wanted for population control of organisms). It is only for the second of these two categories that Field T-3 is coded with symbols of the 1-- series; the distinction is made by not coding Field T-3 when a lethal action coded in Field T-2 is undesired.

This might have been accomplished by providing only a single symbol in Field T-3 which would have indicated that the lethal information was of the category as described above (death being intended and desired) and that it was for the test organism coded in Field E. However, the CBCC has provided a list of specific categories and coding of Field T-3 should conform to the categories' descriptions in the Code (herbicide, rodenticide, air-disinfecting agent, etc.).

Included in this series are the two terms, repellent and attractant, which were once coded in Field T-2 as being special states of the test organism brought about by the test compound (states of repulsion and attraction). They are now included in this Field T-3 symbol series on the basis of the fact that the qualities of attractiveness or repellency qualify a test compound for controlling organisms as well as its lethal qualities. When either repellent or attractant (Symbol 116 or 117) is coded in Field T-3, Field T-2 is coded only with Symbol 14.

As indicated above, Field T-3 is coded with a symbol of the 1-- series only when death of the test organism (or repellency or attraction of the test organism) is the desired response; if the compound tested does not cause death, attraction, or repulsion at the dose administered, when death, attraction, or repulsion is the objective of the test, Field T-3 should nevertheless be coded with the appropriate symbol of the 1-- series and evaluation in Field Y should be based on the compound's ability to kill, attract, or repel (evaluated as negative in Field Y). Furthermore, in such tests in which death, repellency, or attraction is the desired response and the test compound proves to produce an effect opposite to the desired response (increase of infestation instead of death, attraction instead of repellency, repellency instead of attraction), two code lines should be prepared, one with Field T-3 coded to indicate the death, repellency, or attraction desired and evaluated negatively and a second line with Field T-3 either not coded or coded with the opposing effect actually produced and with evaluation based on that action produced.

2. Symbols of the 2-- series; the general pharmacological category of test compounds' specific physiological effects; the pharmacological use for which the test compound is evaluated.

The explanation of the use for terms of the 1-- symbol series can be applied to terms of the 2-- symbol series. When any test result indicates that the compound tested is candidate for being classed in one of the categories represented by symbols of the 2-- series, Field T-3 should be coded with one of those symbols. When a test method is specifically designed to demonstrate a compound's ability to cause one of the effects of symbol series 2--, Field T-3 should be coded with that category of effect to indicate its being evaluated on that basis, whether the test compound produced the effect or not.

3. Symbols 272 and 273; carcinostatic and carcinoclastic compounds

Symbol 272 implies that a tumor affected by the test compound is retarded but not that it regresses. Only Symbol 273 is used to indicate the regression of a tumor.

Symbol 273 is used when the specific effect coded in Fields T-1 and T-2 indicates that the compound produces a destructive effect on a tumor as judged by loss of transplantability or by regression attributable to action of the test compound.

4. Choice of Field T-3 symbols when either of two (or more) might describe the compound

In cases when either of two items might be appropriate (e.g., anti-rheumatic, Symbol 211, and adrenal-corticoid, Symbol 240), the coder must make the most appropriate choice, depending on the nature of the test or the emphasis of the author's description, rather than prepare two code lines.

5. Symbols of the 3-- series; the general plant-regulatory category of test compounds' specific effects on plants; the plant-regulatory use for which the test compound is evaluated

Symbols of the 3-- series are used ONLY when one of the specific effects of the test compound (Fields T-1 and T-2) occurs in plants or when the compound is tested for one of the specific effects on plants whether or not it proves capable of causing the effect.

6. Symbols available for additional items of Field T-3

There are an enormous number of symbols available for use in Field T-3, even if the restriction were continued that no letters be used for forming symbols of the field.

7. File of coded biology data on IBM punched cards arranged accoring to symbols for categories of Field T-3

The CBCC maintains a file of information punched on IBM cards in which an entry has been made in Field T-3.

8. Double coding in Field T-3

Field T-3 is never double coded.

MISCELLANEOUS TIME VALUES

A. Duration of response
(time after response begins)

1. Duration of response
2. Duration of delay of death
(alteration of survival time)

B. Duration of the period
preceding response

3. Time to response:
3a. Time to any response other than death
3b. Time to death (killing time)

C. Duration of a compound's
ability to produce response

4. Persistence of the activity of a residue of the test compound

Organization

A series of overlapping scales have been prepared for this field (corresponding exactly to the symbols assigned to Field P). Each scale covers a limited time period, each period having been selected in such a way that all data from a single type of test can usually be coded by employing only a single scale in Field U. The first column of this two-column field is used to designate the scale being used and the second column indicates a specific time range.

For a full explanation of the organization of the time scales, see the discussion of the organization of Field P.

General Use

Field U has four basic uses, each having to do with time values concerned with the test compound's action. The several uses do not present problems of conflict (i.e., they do not compete for the use of Field U), since each occurs only with a test situation that excludes the other uses (with the possible exception of Uses 1 and 3a which, however, do not constitute a serious problem of choice). There are distinguishable three general categories of the time values coded in the field, (A) duration of the response, (B) time, after the beginning of administration of the test compound, to the beginning of the specific response, and (C) persistence of activity of a residue of the test compound. The specific uses of the field are briefly outlined below, under these three categories. In this outline, the uses are described as being two specific time periods of Category A (1 and 2), one time period of Category B (subdivided in the list as 3a and 3b, however, according to the specific action being death or other-than-death), and one time period of Category C (4). These four specific uses are each discussed in the Specific Directions and Explanations section.

Field U can be used to express:

A. A time period during which the organism responds to the test compound, the end of the period marking the limit of the test compound's competence relative to the response it induced. The two time values of this category for which Field U may be used are as follows:

1. To express the DURATION OF ACTION of the test compound

"Duration of action" is defined as the period of time, following the end of the application of the test compound to the organism, during which time the test compound

exerts a non-lethal action which is coded in Fields T-1 and T-2. To obtain a duration of action value, observation must be made of the point of return to normal, as well as the point at which the action begins subsequent to the end of administration.

2. To express the ALTERATION IN SURVIVAL TIME caused by the test compound

Use Number 2 represents a duration of action as well as does Use Number 1, as is implied by including them both under Category A. The alteration of survival time (Use Number 2) is the duration of delay of death (in the reverse case of speeding death, the alteration of survival time is equivalent to the duration of delay of death, if the test compound were not administered); the "duration of action" (Use Number 1) is the duration of any action EXCEPT delay of death.

When testing chemicals whose effect is to alter the time of death due to some lethal factor, the test compound's protective or exacerbative effect can essentially begin only at the point that untreated controls die.

B. The time between beginning of administration of the test compound and the appearance of the specific effect coded in Fields T-1 and T-2. In contrast to Category A in which the uses for Field U (Uses 1 and 2) involve time periods after the initiation of the test compound action, the Field U uses included in Category B describe time periods prior to the action. The two uses immediately following are essentially alike and consequently are classified here as a single use (Number 3, separated into 3a and 3b); they differ only in the basic nature of the specific response that the test compound produces at the end of the time period. Field U can be used:

3a. To express the time required to produce a specific response OTHER THAN DEATH. This time value must be coded in Field U when Criterion 10 or 58 is used in Field X.

3b. To express the time required to KILL. This time value must be coded in Field U when Criterion 11 or 59 is used in Field X.

C. The time period over which a given deposit of test compound retains its ability to produce repeatedly a response which was produced on first exposure to the organism, as evidenced from a series of exposures of organisms to the same deposit. Thus, Field U can be used:

4. To express the persistence of action of a compound in a residue test. Inasmuch as this time period represents information about the test compound that is essentially accessory and unrelated to information in any other coding field of the biology code line in which it is entered, the entry of the value is always distinguished as an irregular use by accompanying it with Symbol * in Column 66.

The coder's selection of an appropriate Field U scale depends on the same factors as are used in selecting an appropriate scale of Field P. This is explained in Division 1 of the Specific Directions and Explanations of Field P, to which reference should be made.

Specific Directions and Explanations

1. Duration of action; coding in Field U with Field X Criterion 13 or 54

Duration of action is defined in the section above, General Use (see specific Use Number 1). Note that when the response coded in Field T is not actually produced by the test compound, Field U could not be coded with "duration of action" (nor could Criterion 13 or 54 be used in Field X), since the action was non-existent, though Field V ("time of evaluation" which, with negative data, is actually duration of observation) could be coded. Also note that the definition for "duration of action" specifies a test compound administration of limited duration, only after the end of which can begin the "duration of action" period; when administration is continuous, "duration of action" is not an applicable concept, since the action could only (1) continue at a level as long as administration continued, in which case the duration would be a meaningless measure, or (2) increase with time, which would be

indicative of sensitivity increase or cumulative effects, or (3) diminish with time, which would imply only fatigue or tolerance increase. Finally, note that death or any response that ends in death can not be measured in terms of "duration of action" and in case of such lethal actions, Criteria 13 and 54 can not be used nor is there a duration of action value possible in Field U. In addition to death, certain other items of Field T-2 represent self-terminating processes (e.g., organ destruction) for which the duration of the test compound's effect can not be measured, since that effect is apt to be merely initiatory.

In a test for a duration of action value, there may be an appreciable interval between the end of administration of the test compound and the beginning of the response. This interval is actually the "time to specific action" and the duration of action value should not include this interval when it is known. When the "time to specific action" is known, Field U may be used to code this value (explained in Division 3A below) and must be used if evaluation is based on it (Criterion 10 or 58 of Field X). However, if duration of action (the first appearance of the response to its end) is the basis of evaluation (Criterion 13 or 54 of Field X), it is that time interval that must be entered in Field U rather than "time to specific action".

If the response appears (1) prior to the end of the administration of the test compound or (2) simultaneously with the end of administration, or (3) after such a brief period that, relative to the duration period, the interval is insignificant, the duration of action period is considered to begin at the end of administration. If there is known to be an interval between the end of administration and the beginning of the response, yet the length of this interval is not given, the CBCC has considered the duration of action as beginning with the end of administration, though it is preferred to code the actual duration whenever possible as explained in the previous paragraph.

Duration of action, as defined above, should always be coded in Field U when it is known, even if the criterion for evaluation in Field X is not "duration of action" or, if Field U must be used for coding time to specific action because Field X has been coded with Criterion 10 or 58, and a duration of action value is known, the latter should be included in the written abstract portion of the field.

When a test compound affects an organism so that the direction of action reverses (Symbol 4 or 5 of Field T-1), there would necessarily be two "durations of action", the duration of the increase and the duration of the decrease, although the entire period of the chemical influence, including both the increase and decrease, might conceivably be considered to represent a single "duration of action". When Field T-1 is coded with Symbol 4 or 5, evaluation should never be by Criterion 13 or 54 of Field X, since the circumstances would be unusual or improbable when it would be meaningful to evaluate the chemical on the basis of the total period of time over which it has produced a sequence of opposing effects. Consequently, when Symbol 4 or 5 is used in Field T-1, the CBCC has established the rule that Field U should never be coded with either the duration of increase or the duration of decrease of action; both values should be included in the written abstract portion of Field U and the code boxes should be cross-hatched.

If the test has been performed expressly to determine a duration of action, the time period is apt to be expressed by the author so that the CBCC coder need not be concerned about calculating it; however, lacking an author's statement of a duration of action, but having information in the form of charts, tables, Kymograph records, etc., which permits deriving the desired time value, the period should be considered to end at the time of the first observation of the organism's return to normal, even if an interval has lapsed between this observation and the previous observation and it is not known exactly when during this interval the organism returned to normal.

2. Alteration of survival time by the test compound; coding in Field U with Field X Criteria 12 and 57

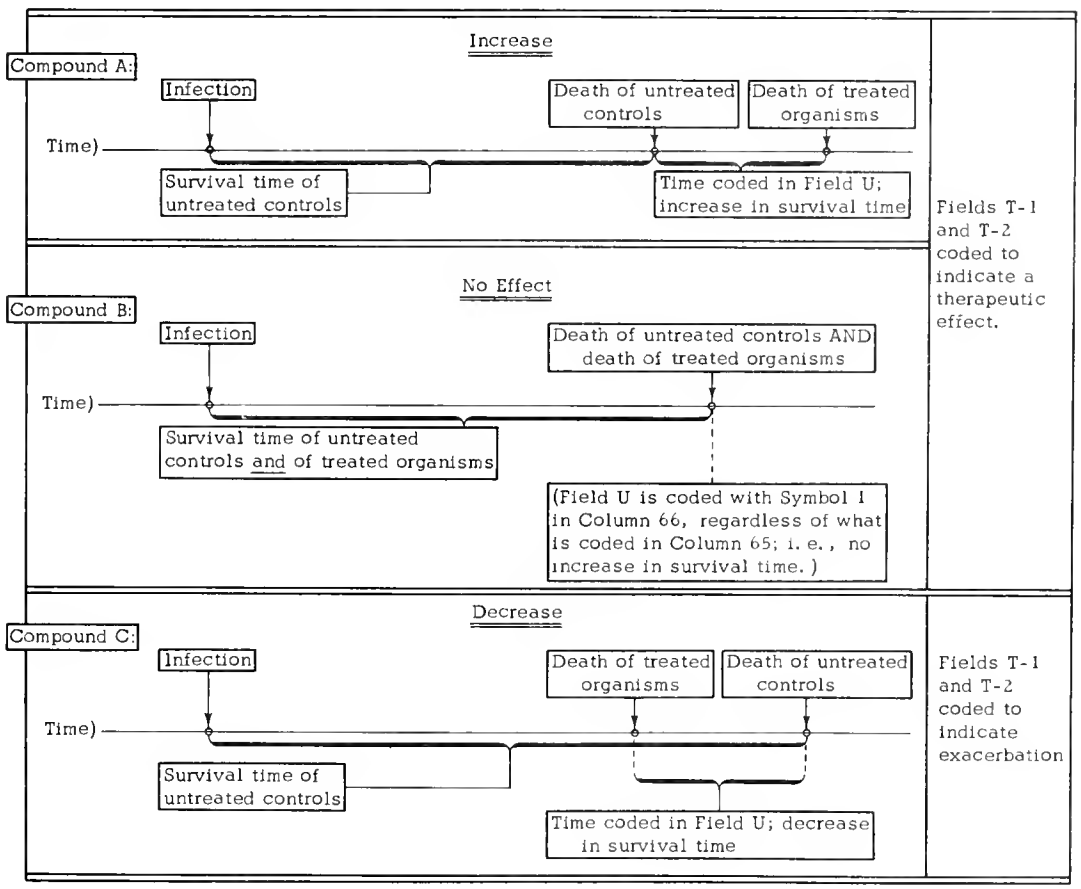
The test compound's effect on survival time is defined above in the section on General Use (see specific Use Number 2). When either Criterion 12 or 57 is to be used in Field X, Field U must be coded with a time value representing an increase or decrease in survival time (or with a symbol representing no increase in survival time, Field U Symbols 11 or 91, e.g.). If the test compound increases survival time, a remedial or ameliorative effect is indicated and Fields T-1 and T-2 are coded accordingly (Symbol 1 in Field T-1 and Symbol 12 in Field T-2 or Symbol 7 in Field T-1 and Symbol 1753 in Field T-2, according to whether or not the time value is an increase in duration of viability or an increase in time of survival of pathology); even if the test compound produced no change in time, as compared to untreated organisms, Fields T-1 and T-2 can be coded with the therapeutic action for which the test

compound was candidate as indicated above, in which case Criterion 01 must be used in Field X, with Fields U and Y coded with Symbol 1 in Columns 66 and 71, respectively. If the coder were to have only the information that the survival time or duration of viability was increased, without an actual time value to code in Field U, the field can not be coded and the evaluation must be by Criterion 01.

However, if the test compound decreases survival time and the author does not specifically indicate that it is due to the compound's toxicity, the only interpretation that should be given by the CBCC coder is one of exacerbation of the situation causing death of the organism whose survival was foreshortened under the conditions of the test. It should not be interpreted by the coder as toxicity to the host; determination of toxicity and toxic dose levels should properly be made in organisms not suffering a fatal condition. In such situations, therefore, Fields T-1 and T-2 can only be coded with the symbols for accelerating the pathology's action (Symbol 2 in Field T-1 and Symbol 12 in Field T-2 or Symbol 7 in Field T-1 and Symbol 1621 in Field T-2, according to whether or not the time value is an increase in duration of viability or an increase in time of survival of pathology), Field U should be coded with the decrease in survival time, and evaluation should be positive (inasmuch as the action is coded in Field T as exacerbation) in Fields X and Y, using Criterion 12 or 57. As explained above, if the author provides no actual time value nor data for calculating a decrease in survival time or decrease in duration of viability, Field U can not be coded and the effect must be evaluated by Criterion 01.

Administration of the test compound can be continuous in testing for effects on survival time, whereas, as explained in the previous division, a duration of action value can not be determined from a test in which administration is continuous.

Alteration of survival time as coded in Field U is illustrated graphically as follows; administration of the test compound is not included in these diagrams. It may occur before or after infection and it may be of limited duration or it may be continuous:



In selecting a scale for coding the test compound's alteration of survival time in Field U, choose the scale whose intervals represent increases or decreases over untreated controls that seem reasonably to be significant. For example, if untreated controls die at about the 24th hour, Scale 8 would not be a very appropriate choice for Field U, because the shortest increase in survival time of Scale 8 that would permit a coding evaluation showing any significant action of the test compound would be 100% increase or more (Symbol 2, 24 hours to 2 days). A more appropriate scale for this example would be Scale 5. Listed below are sample control survival times for which are suggested Field U scales.

Survival time of untreated controls	Scale
10 seconds	1 (or 2)
1 minute	2 (or 3)
10 minutes	3 (or 4)
1 hour	4 (or 5)
12 hours	5 (or 6)
1 day	5 (or 6)
3 days	6 (or 7)
5 days	7 (or 6 or 8)
1 week	9 (or 8)
10 days	9 (or 8)
>2 weeks	9

3. Time to specific action; coding in Field U with Field X Criterion 10, 11, 58, or 59

Between beginning of application of the test compound and manifestation of response, there is conceivably always a time interval, even if it is often extremely brief. This interval may be due to any of several factors other than an ability of the basic biological system for rapid response; for example, it may reflect in part the time for distribution of the chemical from the point of administration or the time for physical passage into cells, etc. In any case, the interval sometimes bears significance for purposes of comparative evaluation and when this evaluation is made (Criteria 10, 11, 58, or 59 in Field X), Field U is used to record the time interval value, as explained in Subdivisions A and B below.

A. Time to specific action OTHER THAN DEATH; coding in Field U with Field X Criterion 10 or 58

When a test is evaluated according to the time needed to produce a given response other than death (even though death may follow this particular response, after another time interval), the time from the initial application to the first appearance of the response must be coded in Field U.

Note carefully that this time to specific response coded in Field U terminates with the first appearance of the response; it is not the time to some subsequent degree of response (e.g., not the time to peak of the response or at a given time after application begins). Field V is used, rather than Field U, to code the "time of evaluation" regardless of whether evaluation is at the beginning of the specific action or after (or even before) the action begins. In the case of making code evaluation by Criterion 10 or 58, the "time to specific response" is also the "time to evaluation" and Fields U and V are coded with the identical time values (though not with identical code symbols).

When evaluation is made at some point after the beginning of a specific action (i. e., by a criterion other than Criterion 10 or 58, such as Criterion 01, 02, 03, 04, or 62), yet between the application of the test compound and the beginning of the response there has been a period of known duration, the question arises as to whether to record this latter time period in Field U, since it is not to be used with Criterion 10 or 58 for evaluation. The CBCC does not code the value in Field U under such circumstances, since, without some extra indicator (such as a zone punch in Column 65), the meaning of an entry in Field U can not be determined without Criterion 10, 11, 12, 13, 54, 57, 58, or 59 in Field X.

Whether the administration has been a single or multiple terminated application or has been continuous up to the first manifestation of response bears no influence on the value coded in Field U as the time to specific action other than death (Criterion 10 or 58) or as the killing time (Criterion 11 or 59).

If a given response for which a chemical is being specifically tested does not occur (i. e., if the results are negative), evaluation can not be made by Criterion 10 or 58 and, accordingly, Field U can not be coded with a time value; only Field V might be coded with the period of observation.

B. Killing time; coding in Field U with Field X Criterion 11 or 59

When a test is evaluated according to the time taken to produce death (even though death may be preceded by one or several other specific responses), the time from the initial application to the death of the organism must be coded in Field U. If death does not result, when the aim of the test was to find the lethal level, Criterion 11 or 59 can not be used in Field X and, correspondingly, Field U can not be coded with a time value; only Field V might be coded with the period of observation.

4. Persistence of activity of a test compound as a residue; demonstrations of persistence of activity of a residue and evaluations thereby are never coded except that this persistence of activity value (i. e., the time period over which a test compound retains its ability to produce a response) may be coded in Field U, where it is distinguished as representing a unique use of Field U by coding with it Symbol * in Column 66

Chemicals are not infrequently applied to a substrate with the intent of affecting specific organisms which subsequently contact the coated substrate. The manner of such application varies; e.g., spreading the pure compound--or the compound in a paste--over the substrate or applying the compound in a volatile carrier which evaporates to leave the chemical as a deposit. In any case, the material represents a residue whose effect on a biological system is evidenced only after an organism makes contact with the residue, which may occur only after a considerable lapse of time. Thus, a time factor is interposed which is unrelated to a biological organism and relates only to the chemical--the period over which the chemical retains its ability to produce a given response when an organism contacts it. This may be a measure of its chemical stability or of its resistance to physical change such as congealing, solidification, evaporation, etc. Regardless of what occurs to the chemical between the time of application to the substrate and the time of contact with an organism, any intervening alteration of the chemical can not be a biological activity nor a measure of biological activity.

The procedure of determining the persistence of activity of a residue usually consists of performing a series of tests on the same residue, exposing one or more test organisms to the residue at given intervals after its deposit on the substate. Because these tests involve living organisms and the author evaluates the compound on the basis of its ability to retain its efficacy as a residue, there is a strong temptation to construct a biology code line in an effort to code in the evaluation code fields (Fields W, X, and Y) the author's persistence evaluation. This is no more consistent with the purpose of the CBCC coding of biological factors than to evaluate the chemical on the basis of its photostability, or its relative cost, or the desirability of its odor.

Rather than dismiss such test results entirely, the CBCC codes the data in the following manner.

A. A code line is constructed for the results of the first test of the series of tests demonstrating persistence of the residue, since this first test measures, more accurately than later ones of the series, the actual biological activity. In this code line, the biological response is coded in Field T and the code evaluation depends on how much data is given by the author for that first test. If per cent response, per cent kill, or comparison to action of a standard compound are given, evaluation may be by that value. Otherwise, evaluation can be only by Criterion 01 in Field X, and Field Y is coded to represent the degree of response in that first test--never to represent the author's evaluation of the test compound residue based on its relative persistence as demonstrated by subsequent tests of the series. There is no way of coding collectively the entire series of tests in a single code line and consequently no way of coding the evaluation of the persistence of activity of the test compound as a residue.

B. The CBCC, however, has made a special provision for recording this time period (though not an evaluation based on the time period) over which a test compound has been demonstrated to retain its ability to produce a given response: IN THE SAME CODE LINE DESCRIBING AND EVALUATING THE FIRST TEST (OF THE SERIES DEMONSTRATING THE PERSISTENCE OF ACTIVITY OF THE RESIDUE), THE PERSISTENCE OF ACTIVITY OF THE RESIDUE (I. E., THE PERIOD FROM THE TIME OF APPLICATION TO THE SUBSTRATE TO THE TIME OF THE LAST TEST IN WHICH THE TEST COMPOUND PRODUCED A RESPONSE IN A TEST ORGANISM) IS CODED IN FIELD U. Inasmuch as this value is essentially accessory to the rest of the coded information of that code line and is never related to the evaluation coded in Fields W, X, and Y, it is necessary to distinguish it from the more conventional use of Field U (see Divisions 1, 2, and 3, above); this is accomplished by coding the Symbol * (i. e., the 12 zone punch) in Column 66 of Field U with the persistence of activity of residue value.

Since the persistence of activity of a residue is only accessory information, the code line represents only the action of the test compound on the test organism, and for this reason Field X can be used only to evaluate that test organism's response and is never used to evaluate the test compound's persistence. Therefore, if the author compares the test compound's persistence as a residue to a standard compound's persistence as a residue, this comparison can never be coded but the information should be included in the written abstract. An attempt should not be made to use Criterion 03 or 04 nor to code this standard compound in Field D, since this would be interpreted as stating that the secondary compound was a standard for the effect coded in Fields T-1 and T-2 rather than a standard for persistence of a residue. (See also Division 6 of the Specific Directions and Explanations for Field O.

5. Coding of persistence of activity of a residue when the measure is in terms other than time

Occasionally, the durability of a residue of a test compound may be tested by treating it repeatedly with any of the physical factors to which it might normally be exposed. Thus, the residue might be repeatedly rinsed with water (simulating exposure to rain, tide, spray, etc.) or radiated (simulating exposure to sunlight), etc. The results are subsequently expressed, not in terms of time, but as the number of washings or the amount of light, etc., necessary to reduce the chemical's activity. Thus, such persistence of activity of a residue can not be coded in Field U, for lack of suitable code expressions; nevertheless, Field U should be used for the purpose of recording these data by coding the field with Symbol * only and explaining by the written abstract the test compound's endurance of the treatment.

6. Choice of scales and ranges for coding in Field U

Appropriate selection of scales in Field U has already been specially discussed for coding alterations in survival time (Division 2, above).

For coding durations of action, time to specific action, time to death, and persistence of activity of a residue (Divisions 1, 3, and 4, above) care should similarly be exercised in selecting appropriate scales. The explanation of selection of scales for Field P (Division 1 of the Specific Directions and Explanations section for Field P) applies equally to selection of scales in Field U and reference should be made to that discussion.

When a time value is given in terms of an indefinite range of values (e. g., "the ability of the test compound to cause a specific effect persisted for one to two months"), code an average value (in the example given, 6 weeks).

A Field U time value may be expressed only as a general range (e. g., "the response lasts from 'X' to 'Y' hours"). In particular, the range, 24-48 hours seems so common that the question has frequently arisen as to how to code it. It is recommended that it be coded by the symbol representing >24 hours through 48 hours rather than to double code in Field U both the symbols for >12 through 24 and >24 through 48.

7. Relationship between Field U and Field P (duration of administration of the test compound)

When Field U is coded with time to specific action, or "killing time", or "alteration of survival time" (Criterion 10, 11, 12, 57, 58, or 59 of Field X), the coding in Field P should always be consistent with the coding in Field U, in the following respect. A duration of administration coded in Field P should never be longer than a "time to specific action other than death", or a "killing time", or a time of death of the organism whose "survival time has been altered" coded in Field U--even if the test were run by a standard technique in which the administration was routinely over a longer period or if, in the case of making evaluation by "time to specific action other than death", administration had actually continued beyond the beginning of response. This aspect of Field P is discussed in a general way in Division 2 of Specific Directions and Explanations of Field P.

When Field U is coded with a duration of action (Criterion 13 or 54 of Field X), the administration must have ceased prior to the action, else the action's duration could not be assessed; therefore, when Criterion 13 or 54 is used, Field P is always coded with the actual entire duration of administration.

8. Relations between Field U and Fields X and Y; use of the code symbols of Field U for evaluation

While the information coded in Field U is in a sense independently important, just as the information of any other coding field (the test organism, the dosage, the route of administration, etc.), it is at the same time so intimately linked with the coded evaluation in Fields X and Y that the two coding areas are often mutually dependent. To summarize: The previous divisions have explained that if Field X is coded with "duration of action" (Criterion 13 or 54), the value coded in Field U can be only duration of action; if Field X is coded with "time to specific action" (Criterion 10 or 58) or "killing time" (Criterion 11 or 59), the value coded in Field U can be only time to specific action or killing time (with an exception explained in Division 9); if Field X is coded with "alteration of survival time" (Criterion 12 or 57), Field U can be coded only with alteration of survival time. The significance of this is that the meaning of the entry in Field U is distinguished only by the coding in Field X or the Symbol * in Column 66. Without the appropriate coding in Field X, an entry in Field U is ambiguous. Therefore, if Field X is coded with none of these eight criteria, Field U is ordinarily not coded, with the exception that it may be coded with "persistence of activity of residue", under conditions described in Division 4, or it may be coded with a duration of action, if this is known, as explained in paragraph 4 of Division 1.

When evaluation is by any of Field X Criteria 10, 11, 12, 13, 54, 57, 58, or 59, the code symbols of Field U are used to derive the evaluation symbol to be coded in Field Y. Criteria 10, 11, 12, and 13 base evaluation solely and directly on the time value coded in Field U. The coding procedure in these cases is simply to use for Field Y the value coded in Column 66 of Field U--or the reciprocal of that value--as follows:

Field X	Field Y
Criterion 10	The reciprocal of the value coded in Column 66
Criterion 11	The reciprocal of the value coded in Column 66
Criterion 12	The value coded in Column 66
Criterion 13	The value coded in Column 66

Criteria 54, 57, 58, and 59, however, base evaluation not only on the time value coded in Field U, but also on the per cent of organisms responding, from which association there results a value used as a code evaluation in Field Y, as follows:

FIELD U
Columns 65 and 66

Field X	Log-probit Grid	Field Y
Criterion 54	Reciprocal of the value coded in Column 66 (on abscissa) --vs. cumulative per cent organisms responding (on ordinate)	Values, derived from plotting on the Grid.
Criterion 57	Reciprocal of the value coded in Column 66 (on abscissa) --vs. cumulative per cent organisms responding (on ordinate)	
Criterion 58	The value coded in Column 66 (on abscissa)--vs. cumulative per cent organisms responding (on ordinate)	
Criterion 59	The value coded in Column 66 (on abscissa)--vs. cumulative per cent organisms responding (on ordinate)	

These criteria are discussed in detail in the Specific Directions and Explanations section for Fields W, X, and Y, Division 20; the illustrations at the end of that division should be studied to understand the plotting of the cumulative per cent of organisms on the ordinate of the Grid.

9. Conflict between uses of Field U: persistence of activity of residue vs. any of the time values used for evaluation coded in Fields X and Y

In the event that the response to the test compound residue is evaluated by "killing time", "time to specific response", or "duration of action" (each of which would require an entry in Field U) and the persistence of the activity of the residue has been determined, a conflict arises in the use of Field U.

This conflict is resolved by the provision always to use Field U for coding the persistence of the residue when it has been demonstrated. This is permitted for the following reason. Even though Field U is occupied with a persistence-of-activity-of-residue value (as will be evidenced by Symbol * in Column 66), Criterion 10, 11, 58, or 59 (but not 13 or 54) can be used--by virtue of the fact that the "time to specific action" or "killing time" is always identical to the "time of evaluation" which is coded in Field V; thus, when Criterion 10, 11, 58, or 59 is used in Field X and Symbol * appears in Column 66, the time value in Field V represents the "time to specific action" or the "killing time" as well as "evaluation time". The coding in Field Y in this case would be derived by consulting the code scales of Field U to determine the coding that would have been in Field U had it not been occupied by persistence-of-activity-of-residue data. Note, however, that coding in Field V is not identical to a "duration of action" (Criteria 13 and 54) and if Field U is occupied with "persistence of activity of a residue", there is no way to code a "duration of action". Therefore, when persistence of activity of a residue is coded in Field U, Criterion 13 or 54 must not be used in Field X; this is little disadvantage, since it is so improbable that in a typical test for persistence of residue, an evaluation of the individual tests would be made on the basis of duration of action. If this latter conflict should arise, construction of a second code line is recommended in which the duration of action would be coded in Field U, Criterion 13 or 54 used in Field X, and, in the written abstract of Field U, attention would be called to the preceding line in which is coded the persistence of residue.

This CBCC choice of giving precedence to the persistence-of-activity-of-residue information was due to the coding initially of a large amount of insecticidal data, for which persistence-of-activity-of-residue data are particularly important. It is suggested that for projects other than the CBCC, a precedence might be given to other information for Field U or the procedure established of coding a line for each time value for which Field U is used.

10. Symbols available

Although the ten scales now in Field U are fairly exhaustive of the time ranges expected in most chemical-biological tests, letters J through Z are available in Column 65 for any new scales needed. The CBCC restricts time range coding to numerical symbols (i.e., Symbols 1 through 9) to correspond to evaluation ranges in Field Y.

11. File of IBM Punched Cards

No file of coded biology data has been established, arranged by Field U entries. Information coded in Field U is of such a nature that sorting for it is almost invariably subsequent to retrieval of information by specific actions, test organisms, test compounds, etc. (for which there are special IBM files).

12. Double coding

Field U should never be double coded when using Criterion 10, 11, 12 or 13 in Field X. However, when evaluation is based on the incidences (in a group of organisms) of several time values (several durations of action, several time periods to specific action, etc.) and the Grid is used (Criterion 54, 57, 58, or 59), Field U can be double coded, if necessary, to show the upper and lower time limits within which range are all the time values giving the evaluation coded in Field Y.

Symbol * can be entered in the same code box (Column 66) as the coding of a time value, as explained in Division 4.

Double coding is permitted in Field U under the conditions described above, but only in Column 66. When Field U is double coded in Column 66 or when Symbol * is coded with another symbol in that column, both coded symbols are punched on the same IBM card in that column.

TIME TO EVALUATION

Organization

As in the case of Fields M, N, P, Q, and U, the quantitative numerical values for Field V (time periods) are reduced to single-unit symbols for accommodation by a single punched card column. For example, Symbol 2 represents any period of time within the range of 0.5 second through 1.0 second; Symbol L may represent any time period from 4 through 8 days.

The several ranges of time periods have been organized to give a logarithmic progression from a very narrow range for brief periods (e. g., 0.5 second through 1 second, a range of 0.5 second) to correspondingly appropriate ranges for longer periods (e. g., >16 months through 32 months, a range of 16 months).

The list of code symbols and their definitions is broken into four groups corresponding to the standard IBM punch combinations that form the symbols. (Numerical symbols, 1 through 9, require no IBM zone punch; Symbols A through I are formed by use of the 12 zone punch; Symbols J through R are formed by use of the 11 zone punch; and Symbols S through Z are formed by use of the 0 zone punch.) The reason for this separation in listing is explained in the discussion on double coding, Division 8, of the Specific Directions and Explanations below.

General Use

Field V is used to code the period of time needed to produce a response (Fields T-1 and T-2) to a given degree (Fields W, X, and Y). In other words, this is the period of time beginning at the initiation of treatment and ending at the point when the observation or measurement was made on which was based the evaluation of the response.

Note that "time of evaluation" is not synonymous with "duration of observation" which may extend far beyond the point at which the response is evaluated. Consider a response which began two minutes after administration of the test compound, reached a peak four minutes later, remained at a plateau for 10 minutes, and took 30 minutes thereafter to return to normal, when observation ended; evaluation was based on the greatest degree of response (i. e., at peak action). In this example, the period to evaluation (Field V) is six minutes, whereas the duration of observation is 46 minutes. The CBCC has no provision, nor has it a need, to code the duration of observation (except coincidentally, as explained in Division 2).

Specific Directions and Explanations

1. Relation between Field V and Fields X and Y

The time period coded in Field V (time between beginning of administration and the point of evaluation) is never used as a basis for evaluation by any criterion in Field X, as the time periods in Field U are; on the contrary, the entry in Field V is dependent on when the response is evaluated. For example, if ten observations are made at intervals of several minutes during a test and evaluation (Fields X and Y) is based on the fourth observation, the time period coded in Field V ends at the point of the fourth observation; if the evaluation were based on the ninth observation, the time period coded in Field V would end at the point of the ninth observation. (In this example, where evaluation is based on some observation other than the last, the period ending with the last observation would not be coded, because there is no coding field specifically for "duration of observation".) Ordinarily, in such a series of quantitative observations, evaluation is made (and the "time to evaluation", in Field V, ends) at the point of peak action, though it may be made at the end of a pre-determined optimal time (which will consequently be the "time to evaluation") or at the point of some particular degree of action other than peak action. If evaluation is made according to more than one of these (e. g., [1] evaluation based on the intensity of response 10 minutes after administration and [2] maximum intensity of response regardless of time), two times to evaluation are involved in the same test. This does not involve a double entry in Field V, because two evaluations have been made using

different criteria and only one evaluation criterion is possible for each code line; if both evaluations are to be coded (intensity of response after 10 minutes and maximum intensity of response), two code lines will be necessary in each of which will be coded the appropriate time to evaluation.

In the case of those tests evaluated by "time to specific action other than death" (Criterion 10 or 58) or "killing time" (Criterion 11 or 59), evaluation is necessarily at the point of beginning of the specific action or at the point of death. The "time to specific action" or "killing time" is therefore identical to "time to evaluation" and Fields U and V would be coded with the same values (though not with the same code symbols). Refer to Division 3 of the Specific Directions and Explanations for Field U.

On the other hand, tests evaluated by "alteration of survival time" (Criterion 12 or 57) or "duration of action" (Criterion 13 or 54) have periods of "time to evaluation" (Field V) quite different from the periods coded in Field U. The "time to evaluation" of an alteration-of-survival-time test begins with administration of the test compound and ends at the death of the treated organism, whereas the coding in Field U represents a period which is the difference between the survival times of the treated and untreated organisms. The "time to evaluation" of a duration-of-action test begins with administration of the test compound and ends at the point of the disappearance of the action, whereas the coding in Field U is a period beginning at the first appearance of the action and ending at its disappearance.

2. Coding in Field V when the test compound produces no biological response

If the test compound produces no response, or fails to produce a specific response for which it is being tested (coded in Fields T-1 and T-2), the entire period of observation is coded in Field V.

3. Tests for persistence of activity of a residue of the test compound; coding in Field V

Reference should be made to the explanation of persistence of activity of residue tests, in Division 4 of the Specific Directions and Explanations of Field U. In coding the data of the first exposure to the residue, Field V should be coded with the period beginning at the time the test organism contacts the residue (not beginning at the time of application of the residue to the substrate) and ending with the evaluation of the response of the test organism (not ending with the evaluation of the test compound's persistence as a residue).

4. Prophylaxis studies; coding in Field V

In coding evaluation time for studies of prophylaxis, the beginning of the period to be coded in Field V is the time at which the first dose is administered to the host, even though invading organisms are not yet present.

5. Coding in Field V when the exact time of evaluation is not known, but an approximate time of evaluation is known

Frequently a test procedure will not allow continuous observation, or continuous observation is inconvenient, and, during an interval between two observations, peak action or final action occurs. A common example is the death of an organism (or the death of the last of a group of organisms killed in the test) which occurs sometimes between two observations. Since the exact time of the death can not be known, the exact end of a "time to evaluation" period is unknown. In these cases, the CBCC has coded in Field V a time period ending with the first observation after the death or peak action.

6. Symbols available

All available symbols have been assigned definitions in this field.

7. File of IBM punched cards

No file of IBM punched cards has been established, arranged by code entries in Field V.

8. Double coding

It is possible that more than one measure of activity or point of observation may fall within the range of evaluation assigned to one symbol of Field Y, yet for each of these the time to evaluation would be different. The following two examples will illustrate this. (1) Ten minutes after administration of a test compound, the response was read as 42% increase over normal; 10 minutes later, it was 44%; subsequent readings at 10 minute intervals were 46%, 42%, 10%, and 1%. In this case, the coding of Field Y would be of the highest activity (46% increase over normal), yet the symbol of Field Y which codes this (Symbol 4 of Criterion 62), by the broadness of its definition, actually represents any of 42%, 44%, 46%, and 42%. The period over which the response remained within the levels represented by the symbol of Field Y was from 10 minutes after administration through 40 minutes after administration (four "times to evaluation"). (2) A second example is that of several separate tests of the same compound, differing only in "times to evaluation"; if the results of two or more of these tests are so similar that they are all represented by the same symbol in Field Y, the same situation exists as in Example 1 above; i.e., the code symbol in Field Y represents evaluations from several "times to evaluation". Because of the dependency of Field V on Field Y, Field V can be coded with time periods no more precise than the coding in Field Y; therefore, under the circumstances illustrated by these testing situations, it would be correct to code in Field V all the time-to-evaluation values (i.e., "double code" all the values) which correspond to those evaluations coded by that single Field Y symbol. Unfortunately, double coding is limited in Field V, due to inherent difficulties in mechanical sorting and interpretation when certain symbols are combined. Double coding is permitted in Field V only when the two or more "times to evaluation" are in the same group of symbols (of the four groups in the Code). Double coding of symbols from two groups is not possible, as illustrated by the two values, 1-1/2 minutes and 7-1/2 minutes, for which the code symbols would be 9 (Group 1) and B (Group 2). The punches for these two symbols on the IBM card would be 9, 2, and the 12 zone punch (2 combined with the 12 zone punch represents Symbol B). In interpreting this punching, there is no way of knowing whether the 12 zone punch is meant to be combined with the 2 punch (= Symbol B) or with the 9 punch (= Symbol I). In most cases, however, when it would be desirable to double code in Field V, double coding is not frustrated by this limitation, because in any single type of test, the times of evaluation are apt to occur within only one of the four symbol groups. When the situation arises in which double coding of Field V is prohibited due to the symbols being members of different symbol groups (of the four groups in the Code), two lines should be constructed, identical except for the coding in Field V which will record in one line the shortest time to evaluation and in the other line the longest time to evaluation.

Double coding Field V in the same code line in which another field (e.g., Field P, duration of administration) is double coded is not impossible, but is restricted in that the coding of one of the double-coded fields must bear reciprocal relations to the other, as described in Division 6 of Specific Directions and Explanations of Field P (illustrated there with Fields P and M).

When Field V is double coded, both symbols are punched in Column 67 on the same IBM card. Field V is not a filing field (see Division 7 above), so no problem exists relative to filing the card by one or the other of the two symbols in the column. Having a zone punch combined with two numerical punches in the same column would add complexity to any mechanical sorting in Field V, however. This could be avoided by punching two cards when Field V is double coded with two letter symbols, but so few occasions are apt to occur for double coding with two letter symbols in the field and the machine sorting of Field V is so infrequent or even improbable, the CBCC has not prepared two cards with the Field V double coding punched separately.

EVALUATIONS OF THE BIOLOGICAL RESPONSE TO THE TEST COMPOUND

Organization

These three fields, W, X, and Y, represent collectively a unit for coding one aspect of a chemical-biological test, in the same way that Fields M, N, Ø, and P make a unit for coding dosage and Fields T-1, T-2, and T-3 make a unit for coding biological response of such a test. Fields W, X, and Y are used to code a statement of evaluation of the test results, indicating (1) whether the response did or did not occur, (2) if the response did occur, to what degree or intensity, (3) if the response did not occur, whether the test demonstrated that the chemical CAN not cause the response, and (4) the test compound's potency for causing the response (or its safety in not causing a response that is pernicious), considering the quantity needed. These are all discussed in detail in the following sections on General Use and Specific Directions and Explanations.

Field W, a single-column field (Column 68), has been given eight symbols for the use described in the next section, General Use. Symbols J, K, L, M, N, Ø, P, and Q were chosen because the 12 zone punch (Symbol *) was given a meaning distinct from the other symbols (prohibiting the use of Symbols A through I) and because Field W had been for a different coding purpose for which Symbols 1 through 9 had been used. This former use of Field W is described in the section on General Use. Thus, Symbols J through Q were used rather than Symbols 1 through 8 to avoid confusion with the earlier CBCC use of the numerical symbols by which considerable data had been coded, punched, and filed. (In a newly started coding project, these symbols might well be numerical rather than J through Q.)

Fields X and Y have been organized in the Code so that each symbol for Field X is accompanied by Field Y symbols which have definitions specifically related to that Field X symbol and which must be used with that Field X symbol.

Field X is a two-column field (Columns 69 and 70). Because there is generally advantage in similar items being listed together and in having these similar items represented by code symbols of related order, the criteria have been organized into several groups which can be distinguished by examining the Code. One example of criteria having an evaluating characteristic in common consists of criteria basing evaluations on time values alone, Criteria 10, 11, 12, and 13 (coded as Symbols 10, 11, 12, and 13). Other groups are as follows: Authors' expressions of evaluation (01 and 02), comparisons to a compound which the author has considered sufficiently standard to serve as a reference for activity of a test compound (03 and 04), special indexes for evaluation (14, 15, 16, 17, 18, and 19), dosage criteria basing evaluation on dosage size alone (20, 21, and 22), special criteria for specific actions (30 and 31), those criteria whose evaluation determinations include consideration of dosage values or time values correlated with variation in individuals of a group (51, 52, 53, 54, 55, 57, 58, and 59), and criteria basing evaluation solely on intensity of response, which may be in terms of the percentage of indivlduals in a group responding, (61 and 62). Field X items have been limited to numerical symbols, because it is more practical to do so when the items are few enough to permit it. This is because the IBM processing is always more simple when zone punches need not be used for forming letter symbols.

Field Y, a single column field (Column 71), is ordinarily limited to numerical symbols (the 0 zone punch and Symbols 1 through 9). Thus, as many as ten levels of evaluation of positive activity may be coded. The CBCC considers this as providing evaluation grading to, or beyond, a maximum degree of significance. Inasmuch as evaluation is usually restricted to numerical symbols and the 0 zone punch, the 11 and 12 zone punches were available in Field Y for a special use. This use is described in the section describing the Grid, Division 24 of the Specific Directions and Explanations.

In the case of three criteria of Field X, Criteria 01, 02, and 62, Symbol 1 is reserved for expressing negative data exclusively (see Division 1, Subdivision B, of the Specific Directions and Explanations). Since, with negative data, the 11 or 12 zone punches would never be used (as explained later), the two letters A and J (formed by IBM combination of Symbol 1 plus the 12 or 11 zone punch, respectively) are permitted as symbols for Field Y in the case of those three criteria. This does not represent a retrieval problem relative to the 11 and 12 zone punches, because mechanical sorting for

those particular punches is so improbable; their use in Field Y is only to qualify the evaluation coding they accompany.

The Log-Probit Grid is an adjunct to Fields X and Y, used, in the case of appropriate data, for determining values for Field Y with Criteria of the 5- series (51, 52, 53, 54, 55, 57, 58, and 59). Its structure is described in Division 24.

General Use

This area of the Code is for expressing an evaluation of the intensity of the activity coded in Fields T-1 and T-2 (i. e., the relative ability of the test compound for causing the biological response). The primary need for such a coding area is to provide a way of distinguishing, by code, between instances when a test compound produced the response coded in Field T and instances when the compound did not produce the response for which it was tested. Without this basic distinction, the coding of Fields A through V would be merely a description of the test procedure to determine the test compound's ability to cause the response coded in Field T, with no way of indicating whether or not the response actually occurred.

Beyond the basic need for distinguishing between production of a response ("positive activity") and failure to produce a specific response ("negative activity"), the CBCC has established means of coding grades of positive activity. Certain consistency has been achieved by the CBCC's assuming a leveling policy of "non-interpretation", in other words, a policy of coding, to the extent possible, only the evaluation of the positive response as the author expressed that positive evaluation. To this end, Field X has been provided with the common criteria, as well as some of the more special criteria, used by authors for evaluating positive results of their tests. (No way has been conceived for reducing positive results from tests of all types so that they might all be evaluated by a single common criterion.) Field Y is used to code the actual evaluation (inactivity and levels of activity), based on whatever criterion is coded in Field X.

In addition to the importance of coding the evaluation in order to achieve a complete code statement of each individual test, the evaluation coding is of prime importance to the original concepts and objectives of the CBCC, the correlation of chemical structures and biological responses to those structures. This correlation is conceived as leading to predictions of undetermined biological responses either to a given known chemical or to chemicals of a given structural type and to suggestion of direction of synthesis for new compounds for specific biological actions. In order to make possible the assembly of coded information significant to such correlation and prediction, it is essential that the results of biological tests (i. e., evaluation) of known chemicals be coded, thereby rendering this information capable of being mechanically sorted. Studies of this nature would typically be concerned with the coded evaluations of all biological responses known for which a given chemical was tested or for which chemicals of a given structural type were tested; on the other hand, such studies might revolve about a given biological activity, in which case all compounds known to have been tested for that activity would be assembled to determine if the active (or inactive) chemicals had structural characteristics or physical properties in common.

With this concept in mind, consideration was given to providing a means of recording as precisely as possible the basic capacity of test compounds to cause biological responses. For purposes of explanation, attention is called to the basic coding of "positive" activity (i. e., when the biological response in Field T occurred) vs. "negative" activity (i. e., when the biological response in Field T did not occur), ignoring the problem of coding of the degree of positive response; if consideration is restricted to this simple aspect, it may be more easily understood what is meant by the basic ability of a compound to cause a biological response. Fields X and Y make the distinction between positive activity and negative activity as it was demonstrated under conditions of the test; negative activity is always indicated by one of three criteria in Field X (01, 02, or 62) with Symbol 1 in Field Y; any other coding in Fields X and Y represents positive activity. At first consideration, it might seem adequate to consider that whenever a compound fails to cause a given biological response (coded as negative data) in a given test, it is thereby demonstrated to be incapable of causing the response. Unfortunately, another factor plays a role at the "activity-inactivity" level which, for any given test, is too important to ignore, the quantity of the test compound to which the biological system was exposed in the test being coded. Fields X and Y can code only the response to whatever amount of chemical was administered.

When the chemical fails to produce the response, Fields X and Y can code only the failure of whatever amount of chemical was administered. Many tests are performed with quantities of a test compound below the maximum dose that could be administered, for any of several reasons, but frequently because the compound is available only in small quantities. The only significance such negative test results can claim to have is that, at the dose tested, the response in Field T was not produced. This is never synonymous with having demonstrated that the test compound in adequate quantities (up to a maximum tolerated dose) was inactive in producing the response in Field T.

It will be understood that in interpreting any biology code line, the evaluation is interpreted in the light of all other aspects of the test, including the dose coded in Fields M, N, and P. However, Fields M, N, and P can not reveal what relation that coded dose has to the maximum dose that might have been given--in other words, those fields can not indicate whether it is or not the maximum dose possible or the minimum dose necessary.

For example, there are numerous data from tests for non-toxic responses in which the chemical is administered at or near the maximum dose tolerated by the biological system, toxicity and MTD-determining tests having been run prior to the test being coded. The failure to produce the non-toxic response coded in Field T, when administered at maximum tolerated level, is of much more significance than the failure to produce the response at a lower dose; in essence, the former data imply that, under the conditions of a given test, the test compound CAN not produce a given response in a given organism, whereas the latter data can only state that it DID not produce the response. This distinction is important because of the CBCC's ultimate objective which involves study of the comparative ability of compounds to cause biological response, regardless of the size of the dose necessary to produce the biological response, as well as the relative efficiency (potency) of those compounds demonstrated to cause the biological response, in terms of the dose size needed for that response. To accommodate such distinctions, a coding provision has been made for qualifying the evaluation coding of Fields X and Y; in the case of negative data, for example, Fields X and Y are equipped only to code the fact that a chemical DID not produce a given response, whereas they have no way of indicating whether the test has demonstrated that the compound CAN not produce the response.

The provision for coding the information supplementary to Fields X and Y is made by Field W where eight letter symbols have been assigned definitions for the distinctions Fields X and Y are incapable of making, such as the distinction described in the preceding paragraph. This provision was made recently, replacing an earlier use of Field W. (The former use of Field W is described at the end of this section.) Therefore, very little coding of Field W has been done using the symbols as supplement to the coding of Fields X and Y. Coding of these aspects of test results has not been tried over a sufficiently long period to determine all the associated difficulties nor to assay its ultimate usefulness in sorting, assembling, and interpreting evaluation information for correlation studies. The concepts and definitions of symbols are nevertheless included here in a form expanded from that which has been used by the CBCC. (The use of the symbols is indicated also with the discussion of each criterion of Field X in the section on Specific Directions and Explanations.) This information coded in Field W is largely dependent on results of tests supplementary to the test being coded, such as those prior tests which have determined that the dose administered is or is not a maximum tolerated dose or whether the dose is the minimum effective dose or the response is the maximum of which the test compound is capable.

Of the eight symbols of Field W, Symbol K permits the designation by code that the test has demonstrated the chemical's failure to produce the response at the dose level known by prior testing to be the maximum that can be administered; this symbol therefore indicates that the chemical CAN NOT produce the response. Symbol J is used in Field W for all other negative test results; in other words, it is used when the dose failing to produce a given response is not definitely known to be the maximum dose that might be administered.

In studying chemicals on the basis of their abilities to affect biological systems, especially with the CBCC's purpose of gaining suggestion about other chemicals to test with a given biological system or suggestion about other biological systems to combine with a given chemical, a code provision is important which can distinguish those chemicals which are demonstrated to be so nearly absolutely inactive that they can be removed from consideration. (This particular provision for distinction was not made in Field Y, largely because symbols for that field had been exhausted, having used all numerical symbols and both the 11 and 12 IBM zone punches.)

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Columns 68; 69 and
70; and 71

Field W makes another basic distinction, in addition to the one just discussed, which Fields X and Y are incapable of making; this one also is related to the dose level administered in the test whose results are being coded, but it concerns positive data (i.e., tests demonstrating that the chemical CAN produce a given response). The following brief review of response levels and dosages related to those levels will be helpful in understanding the use of Field W symbols, L, M, N, Ø, and P.

Positive response may be in terms of either (1) an intensity of response of the individual organism or (2) an intensity of response expressed as the number of individuals, of a group, responding at a specified response level (e.g., the number responding by showing a threshold decrease in blood pressure, or 10% increase in growth rate, or cure [100% relief], or death). In either case, a given test compound may cause the maximum intensity of response of which the individual or percentage of individuals of the test organism species is capable of making. On the other hand, regardless of the quantity administered, another test compound may be capable of causing only an intensity of response that is lower than the response the species is capable of making. These aspects of a test compound's action are significant in evaluating its ability to cause the biological response--the ultimate intensity to which the test compound can induce the response (which may be equal to or much lower than the intensity of response the organism is capable of making) and the minimum size of the dose needed to cause that greatest response intensity.

Ideally, for each compound tested for each specific action, it might be desirable to have information, for the individual, about both the maximum response intensity which the test compound is capable of inducing and the minimum dose needed for that maximum intensity, as well as information about threshold intensity and dose. In addition, it might be desirable to know, for each compound and action, the maximum percentage of individuals the test compound can effect, when administered to a population, and the minimum dose needed to affect that number of individuals, as well as information about the smallest number (threshold number) responding to any dose.

All this information is seldom determined or available for any one test compound, because it can ordinarily be determined only by running several tests at different dosage levels, in addition to the specific test being coded; nevertheless, certain types of tests are commonly performed as a series to determine one or more specific levels of response and the minimum doses causing each.

Between the dose causing the chemical's maximum action and the threshold dose, the intensity of response is generally directly proportional to the size of the dose. This direct relationship between threshold dose and threshold response, between doses and response intensities above threshold, and between maximum response of which the compound is capable and minimum dose causing that maximum response is significant. Whether an evaluation is composited by relating the two factors, dose vs. response intensity, or whether evaluation is based solely on intensity of response with the dose causing that intensity coded in Fields M, N, and P, the dose coded in Fields M, N, and P should ideally have been determined by the author to be the minimum dose causing whatever intensity of response is being coded. If not, the evaluation should not be based on the dosage used or Field W should be coded to indicate the fact that the dose was not known to be minimum.

Field W has been furnished with five symbols, L, M, N, Ø, and P, which permit distinguishing whether the response coded in Field T is or is not demonstrated to be the maximum response which the test compound is capable of producing and whether the dose causing the response (coded in Field M or N) is or is not demonstrated to be the minimum dose needed to cause that particular intensity on which the evaluation in Field Y is based. This is information either supplied by the author or evidenced by one or more tests prior to the test which is being coded.

It must be kept in mind that any test compound may, in addition to the response desired, cause other responses. If the desired response is non-toxic (therapeutic or regulatory, e.g.) and if, in addition, the test compound causes death or non-lethal toxic effects, the therapeutic or regulatory response can be produced only to the intensity that the dose size causing that intensity also causes death or other toxic response. In other words, toxicity of a compound may place a ceiling on the dose size that can be administered and on the maximum intensity of non-toxic response; this ceiling may be below the theoretical point of maximum intensity of non-toxic response the organism might make barring the toxicity.

Many chemical-biological test data are concerned with only a single test using only a single dose level. Therefore, much coding in Field W indicating that the response of Fields T-1 and T-2

occurred is simply with Symbol L or, if the single dose level administered is known to be the maximum tolerated, Symbol M.

It is only when the data presented involve a series of tests in which a series of dosage levels have been used that Symbol N, Ø, or P is used.

Symbol Ø is used in any case when (1) the response intensity is demonstrated to be the greatest the compound can produce and (2) the coded dose is known to be the minimum needed to cause that maximum response. Symbol N or P is used when such a series of tests with varying dosage levels has not succeeded in demonstrating one of the following: (1) that the greatest intensity of response produced by the series of tests is the maximum of which the compound is capable (Symbol P) or (2) that the lowest dose tested in the series of tests is the minimum needed to cause the maximum response (Symbol N).

Death itself is unique in that, in the individual organism, there is no "intensity" of death; the minimum dose killing a single individual being tested represents the "peak" of the dosage-response "curve" (a single point) and should always be coded with Symbol Ø in Field W. (This lethal level may be expressed in terms of either the minimum lethal level or maximum tolerated level, but either indicates the level at which death has been demonstrated to occur in the individual.) However, if a group of individuals is treated and the results are expressed in terms of a minimum lethal dose (or maximum tolerated dose), the coding in Field W depends on the percentage of individuals killed in the group. If all (100%) were killed, Field W should be coded with Symbol Ø, but if fewer were killed (i.e., the minimum toxic dose or the maximum tolerated dose for 50% of the individuals), Field W should be coded with Symbol P.

To relate the preceding to Criteria 20 (threshold dose) and 21 (maximum tolerated dose), it will be observed that only Symbol P or Ø may be used with the criteria. When Criterion 20 or 21 is used in Field X and "death" is the response coded in Field T, Symbol P is used in Field W only if administration of the chemical was to a population and the threshold lethal dose kills less than 100% of the population; in all other cases of "death" with Criterion 20 or 21 (when only a single individual is treated or when application is to a population and the threshold dose kills 100% of the population), Symbol Ø is used in Field W.

When Criterion 20 or 21 is used in Field X and the response is any response but "death" (i.e., any non-toxic or toxic-but-not-lethal response), only Symbol P is used in Field W.

For the person assembling and studying data from the CBCC code files, then, either Symbol L, M, or N always means that the compound produced the response at the dose level administered and coded in Field M or N, but that its potency may be underestimated by the interpreter (who would relate the response intensity coded in Field Y with the dose coded in Fields M and N) or understated by the evaluation in Field Y (if the Field Y evaluation were based on a correlation with the dose in Field M or N), since a lower dose might prove equally effective. In contrast, Symbols Ø and P always indicate that a reasonable relationship exists between (1) the coded dose in Field M or N and (2) the intensity of response in Field Y--or that any Field Y evaluation that is based on a correlation between intensity of response and the dose size administered is reasonable; a lower dose would produce a lower response or no response and a larger dose would cause the same response or greater response. Symbol N or Ø indicates that the intensity of response to the dose administered and coded in Field M or N has been the maximum of which the test compound is capable (barring toxicity), while Symbol L or P indicates that the response to the dose coded in Field M or N has possibly been less than that maximum intensity of which the test compound is capable. Symbol M is used when only one dose is tested and it can not be known therefore if the dose is the minimum needed to cause the demonstrated response intensity. Symbol Ø of Field W designates the positive data most significant for comparison of compounds' potencies (i.e., abilities or capacities) for specific actions.

In summary:

	Symbols of Field W
The response intensity coded in Field Y is demonstrated to be the highest response intensity the test compound can cause	M, N, or Ø
The response intensity coded in Field Y is not demonstrated to be the highest response intensity the test compound can cause	L or P
The coded dose is ascertained to be the minimum dose needed for producing the demonstrated response intensity	Ø or P
The coded dose is not ascertained to be the minimum needed for producing the demonstrated response intensity	L, M, or N

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70; and 71

In addition to Symbols J, K, L, M, N, Ø, and P described in the paragraphs above, Field W is used to qualify coding in Field Y by Symbol Q, as explained below in the section of Specific Directions and Explanations, Division 3 and the next to last paragraph of Division 6.

In the development of the Biology Code, Field W was originally used for another purpose, the coding of the slope of the dosage-response curve, a measure of activity of special importance in insecticide studies. As the CBCC program of coding gradually broadened, the need for coding this more special measure, and the use of Field W, diminished to an unrewarding level, corresponding to the lowering percentage of insecticide data coded. Therefore, Field W was converted to its present use to compensate for deficiencies felt in Fields X and Y, as pointed out in the preceding paragraphs. While Field W is no longer used to code slope of the dosage-response curve, the CBCC has continued to demand its being recorded as part of the written abstract, when it is encountered as part of the data. To indicate, by code, that such a written record exists on the Code Sheet, Symbol * (i.e., the IBM 12 zone punch) is coded in Field W. Under these circumstances, a brief explanation of this slope of the dosage-response curve is given below.

With any single, fixed degree of response in the individual organism (e.g., "maximum" response, or "threshold" response, etc., or, in the case of toxicity, "death"), tests can be performed on a group of individuals to determine variation between the individuals of that group relative to the dose size needed to produce that intensity of response; in other words, if variation exists, it will be expressed in terms of variation of dose size producing the given intensity of response, some organisms responding at the given intensity with higher doses, some with lower doses. The tests will determine the percentage of organisms responding (at the given intensity of response) at each of the several dose levels.

By plotting these dosages against the cumulative percent of organisms responding to each respective dose (at a given intensity of response), a curve will be described the slope of which depends upon the test compound and which therefore is descriptive of the test compound's action. The slope of this curve is significant in such studies and is expressed by the standard calculation:

$$\frac{ED_{50}}{\log ED_{84}} \quad \text{or} \quad \frac{LD_{50}}{\log LD_{84}} \quad \text{(when } ED_{50} \text{ [or } LD_{50}\text{] is equated to 1)}$$

$$\frac{\text{(The dose causing the given intensity of response in 50\% of the individuals tested)}}{\text{(The log of the dose causing the given intensity of response in 84\% of the individuals)}}$$

$$\text{Thus:} \quad \frac{1}{\log ED_{84} - \log ED_{50}}$$

Field W was used only when the above calculation could be made; in other words, only when the test compound proved to kill or cause a non-lethal response in at least 84% of the individuals treated. If less than 84% of individuals respond to the test compound at any dose, the slope could not be expressed in Field W. Otherwise the coding could be visualized as describing curves of any slope up to infinity (infinity implying no variation between individuals, but an all-or-none response or death in 100% of individuals at threshold dose). At the time Field W was used for this purpose, the 12 zone punch, Symbol *, was used to indicate that the curve was compound, polymodal, or inflected.

A scale was provided in which calculated slope values were organized into ranges, in the same way that quantitative values of other fields are organized in ranges, and each range was assigned a code symbol. The coding in Field W permitted a discrimination between test compounds whose activity evaluations indicated by coding in Fields X, Y, and the dosage fields were identical or similar.

For every code line prepared, both Field X and Field Y must have an entry. A code symbol in Field Y, without an entry in Field X to explain the terms in which that Field Y symbol expresses evaluation, would be meaningless, as some experience in coding evaluations will demonstrate. Likewise, a code symbol in Field X (stating the criterion on which evaluation is based), without an entry in Field Y (i.e., omitting the evaluation itself), would be unreasonable.

Specific Directions and Explanations

1. Coding of negative data; i.e., coding of failure of the test compound to produce a given response or to produce any response. Use of Field X Criteria 01, 02, and 62, with Symbol 1 in Field Y and Symbol J or K in Field W

   A. "No response of any kind", when the test did not have as an objective the determination of some specific response

In a given test, the test compound may produce no detected biological response of any nature; the organism and its living functions remain unaltered. The results of such a test may be expressed by the author no more specifically.

The expression, "no response of any kind", occurs comparatively infrequently. This is largely because chemical tests are usually performed for production of a specific response, in which case, regardless of whether the chemical did or did not produce any other response, the evaluation is expressed in terms of the chemical's performance in producing or not producing that specific response which is coded in Field T, as explained in Divisions 1B and 2, below.

However, to permit coding the unspecific expression, "no response of any kind", Fields T-1 and T-2 are coded by specially provided symbols, Symbol 0 of Field T-1 and Symbol 1 of Field T-2. (See Division 18 of Field T-1.) While this codes the fundamental fact of "no response of any kind", CBCC coding procedure demands nevertheless that code evaluation be entered in the area especially assigned for evaluation, Fields W, X, and Y. Regardless of which Criterion is used in Field X (it will probably usually be Criterion 01, though it could conceivably be by Criterion 02), Field Y must be coded with Symbol 1 and Field W must be coded with Symbol J (or Symbol K, if the test compound were known to have been administered at its maximum tolerated level).

   B. "No response" or "no effect", relative to a SPECIFIC response for which the chemical was being tested

When a test is designed to determine a compound's unknown ability to produce a specific response, the result of the test may be negative relative to that specific response; in other words, certain compounds will be discovered to be ineffective in producing that specific desired response, regardless of what other responses they may cause. The author will express such negative results in terms of the specific response; for example, "the compound did not cause death", "did not have a repressive action on a disease", "did not increase cardiac rate", "did not decrease cardiac rate", or "had no effect on cardiac rate; i.e., neither increased nor decreased cardiac rate", etc. The CBCC codes these expressions literally; Field T-1 would be coded with Symbol 7 ("causes" or "has"), Symbol 1 ("increases"), Symbol 2 ("decreases"), Symbol 1 and 2 in the same line ("increases and decreases"; i.e., "an effect in either direction on the rate of the specific normal activity"), etc., and Field T-2 would be coded with Symbol 11 ("death"), Symbol 175 ("repressive action"), Symbol C1 ("cardiac rate"), etc.

To record that the specific response coded in Field T was not produced, Field X must be coded with Criterion 01, 02, or 62 and Field Y must be coded with Symbol 1. (Note the definitions and discussion of the terms "no response", "inactive", "negative response", etc., in Division 6.) Field W must be coded with Symbol J (or Symbol K, if the chemical were known to have been administered at the maximum tolerated level).

2. Coding of positive data; i.e., coding the test compound's demonstrated PRODUCTION of a specific response; use of symbols of Fields X and Y (except Symbol 1 of Field Y with Criterion 01, 02, or 62) and use of Symbols L, M, N, Ø, and P of Field W

When the results of a test are positive, the author will necessarily identify the specific response which must be coded in Field T. This is merely to point out that positive data are never reported as "the rest compound produced a response" without specifying what the response was, in the way that negative data are sometimes reported as "no response" (see Division 1, Sub-division A) without specifying a particular response that was not produced.

For any one specific response positively produced, a separate biology code line must be constructed, with the specific response coded in Field T. (The CBCC coding policy often limits the number of specific responses and, correspondingly, the number of code lines to be coded from certain tests characteristically resulting in a complex of many specific responses, as explained in Field T-2, Specific Directions and Explanations, Division 8.)

In this code line for positive data, in which Field T is coded to represent a specific response, Fields W, X, and Y must be coded to relate only to that one specific response which was actually produced by the test compound. Field X may be coded with any appropriate Criterion, including Criterion 01, 02, or 62. Field Y may be coded with any of Symbols 0 or 1 through 9, according to the Criterion used, as indicated in the Code--EXCEPT that Symbol 1 may never be used with Criterion 01, 02, or 62, if the response were actually produced, since this coding is reserved to indicate negative results only (i.e., "no response"), as explained in Division 1. Symbol 1 with any Criterion other than Criterion 01, 02, or 62 is defined and can be interpreted as "positive response, but low in effectiveness", never as "no response".

Field W must be coded with one of the five symbols, L, M, N, Ø, or P, according to what the test demonstrated about the potency of the compound (minimum dose and maximum response intensity) for causing the biological response. (1) If the dose administered is not known to be the minimum dose (below the max. tol. dose) producing maximum response, use Symbol L, M, or N; (2) if the response has been demonstrated to be the maximum which the compound is capable of producing (barring death or limiting toxicity) and the dose is the minimum needed to produce it, use Symbol Ø; (3) if the response has been demonstrated to be the maximum which the compound is capable of producing (barring death or limiting toxicity), but the dose administered is not known to be minimum needed to cause that maximum response, use Symbol M or N; (4) if the response has not been demonstrated to be the maximum which the compound is capable of producing, but the dose administered is known to be minimum for whatever intensity of response was produced, use Symbol P. This is explained in more detail in the previous section, General Use.

3. Coding of questionable test results; use of Symbol Q of Field W

Occasionally, after analyzing his test data, an author will suggest evaluation and at the same time will place a definite qualification of uncertainty on the exactness of this evaluation. Such conservativeness frequently is expressed, for example, when a particular test method, practical for initial screening of compounds, provides a measure of effectiveness too coarse to assure the author that the apparent biological response (or lack of response--or the expressed measure of a specific positive response) should be relied upon. Such data could be dismissed from coding or, if positive, they could be given a vague coding evaluation such as Symbol 0 with Criterion 01--meaning only that "response in some positive degree" was produced. If data on the particular compound or particular organism are rare, however, the data are better coded for what they are worth than lost to the file; furthermore, the author's suggested evaluation is better than one devoid of any rating.

Symbol Q of Field W has been provided merely to express the fact that the author has pointed out that (1) no response was detected, but the particular method of measuring response (or some other factor than dose size and other variables for which the CBCC code line has specific provision) makes this negative evaluation questionable and candidate for further study or (2) a response was detected (coded as positive data in Fields X and Y), but the method of measuring or some other factor makes this positive evaluation questionable; for example, the response observed may not have been due to the compound or may have been only in part due to the treatment, or (3) a positive response was determined which appeared to be quite high (or quite low), but which, due to the method of measure or some other factor, may be less (or more) than this apparent evaluation. Symbol Q is not to be used by the coder to express his own skepticism or questioning of results or of the author's testing method; it is used to express a qualification put on the evaluation by the author himself, when that evaluation suggested by the author is coded literally in Fields X and Y and therefore needs the author's qualification indicated by Symbol Q.

4. Criterion 01; author's evaluation; coder's evaluation (in absence of author's evaluation)

This criterion was established to permit coding those expressions of evaluation consisting of the author's verbal descriptions of response levels, when the author gives no specific measurements which might serve better as coding bases for finer evaluations. (Criterion 02, discussed in Division 5,

was established for essentially the same reason, but deals with author's evaluation expressions in the form of scoring systems rather than verbal descriptions.) With Criterion 01, only five general categories of evaluation have been actually listed and defined for Field Y (plus one for expressing positive action of unspecified degree).

In defining these evaluations, the terms "insignificant" and "significant" have been avoided largely because their use has been found to lead to confusion. Sometimes the term "insignificant" is used to mean that the response was positively demonstrated (i. e., the method of measurement was sufficiently critical to warrant interpreting the measured response as a positive response of specific intensity), but the intensity of response was too low to be considered practical or "significant" for the specific USE for which the author tested the compound. On the other hand, "insignificant response" frequently is used to mean that there was an apparent response, but the conditions of the test or the methods of measurement were such that the measure of response was below the "significant" level; i. e., the measure was considered to be inadequate evidence that the response actually occurred. For consistency, the CBCC has attached the latter definition of "insignificant" to the definition of Symbol 1 (i. e., inadequate evidence that the response actually occurred) and the other definition (positive activity but too low to be practical for a particular use) is attached to the definition of Symbol 3.

The terms listed for these categories of verbal evaluation are not exhaustive of the terms the coder might find used by authors, but terms other than those of the list can be fitted to a symbol by examining the list for a reasonable equivalent to the author's term.

An author's verbal categories may be more or less than the six categories now defined in the Code. For example, there may be only four, "inactive", "slight", "moderate", and "high", of which "moderate" must represent all response intensities from "slight" to "high"; in this case, use of Symbol 6 is indicated for all those responses intermediate between "slight" and "high". On the other hand, still finer categories of evaluation may have been invented by the author (improbable because adjectival terms accurately describing response categories finer than "slight", "moderate", and "high" are limited), in which case Symbols 2, 4, 6, and 8 could be brought into use, in addition to Symbols 5 and 7, for degrees of intermediate intensity of response.

In addition to the use of Criterion 01 as described above for an author's verbal evaluation, its use has been extended (for CBCC coders) to include "coder's evaluation". Criterion 01 should not be regarded as a means of permitting the CBCC coder to express his evaluation of the test result instead of an author's verbal evaluation or instead of using available quantitative data for evaluation according to other criteria. The criterion is, however, intended to permit the qualified coder to evaluate results when the data are not appropriate for evaluation by other criteria in the Code and when the author has not made a definite verbal expression of evaluation.

When the author's verbal evaluation or the coder's judgment are used as entries in Fields X and Y, Field W will be coded according to what is known about the dosage administered and the extensiveness of testing. If no response occurs (Symbol 1 in Field Y), Field W will be coded with Symbol J or K, according to whether the dose coded in Field M or N were known to be the maximum tolerated dose. If the response did occur (symbols other than Symbol 1 in Field Y), Field W will be coded with Symbol L, M, N, Ø, or P, according to what is known about the dose and the maximum intensity of response. If only one dose were tested, Field W would ordinarily be coded with Symbol L or M, according to whether it is administered at maximum tolerated dose. If a series of tests have provided significant information about the dose level administered and the intensity of response produced, Field W may be coded with Symbols N, Ø, or P, according to the definitions of those symbols.

5. Criterion 02; Author's Scoring System

As in the case of Criterion 01, Criterion 02 was established for test results in which the author gives no measurements that might serve as a basis for coding evaluation, but gives only his own estimate of evaluation of the response; Criterion 02, however, is for translating into code symbols arbitrary scoring systems which frequently are used by investigators to scale test responses (in a sense, being the author's own "coding" scheme). The most common scoring system uses simply plus and minus signs, the minus sign representing "no response" or "inactive" and one, two, three, or more plus signs representing increasing degrees of positive response. However, other symbols and devices are used by authors for the same purpose.

FIELDS W, X, and Y
Columns 68; 69 and 70; and 71

In the Code, only five evaluation symbols (Field Y) are defined for Criterion 02 (Field X)--Symbols 1, 3, 5, 7, and 9--, since data consisting only of such scoring systems seldom permit significant division into more than four broad categories of positive activity. Actually, in the case of Criterion 02, this list of five symbols should be considered as an illustration rather than a rigid CBCC evaluation scale; it illustrates the spreading of a sample author's scoring scale (consisting of the author's designations of negative activity and four levels of positive activity) over the total CBCC scale (which consists of a symbol for negative activity [Symbol 1] and Symbols 0, A, and 2 through 9 for ten levels of positive activity). Beyond this illustration, an author's scoring scale having five levels of positive activity or only three levels of positive activity, for example, could also be spread over the total CBCC scale (a scale having only two levels of positive activity is also illustrated in the Code); in doing so, the intervals may be less consistent than in the illustration in the Code, but the coding is nevertheless adequate for the type of evaluation being coded. For sake of consistency in coding, the following CBCC scales (i.e., code symbols of Field Y) are suggested for the possible numbers of levels of authors' scoring systems:

Number of levels of the author's scoring system	CBCC scale of symbols for Field Y
Negative + two positive levels	1, 5, and 9 (See the illustration in the Code.)
Negative + three positive levels	1, 3, 6, and 9
Negative + four positive levels	1, 3, 5, 7, and 9 (See the illustration in the Code.)
Negative + five positive levels	1, 3, 4, 5, 7, and 9
Negative + six positive levels	1, 3, 4, 5, 6, 7, and 9
Negative + seven positive levels	1, 3, 4, 5, 6, 7, 8, and 9
Negative + eight positive levels	1, 2, 3, 4, 5, 6, 7, 8, and 9

Superimposed on the basic arrangement just explained is a percentage scale. (Consult the Code.) Data expressed in terms of a calculated per cent response (0% - 100%) are always coded by Criterion 62. However, there are occasions when an author uses the term "percentage" in a sense of estimate rather than as an expression of accurate measure (e.g., "about 2/3 [i.e., an estimated 66%] of the organisms were killed" or "about half [i.e., an estimated 50%] of the bacterial colonies showed inhibition", etc.). When a biological response is evaluated by such an estimate expressed by the author in terms of per cent (or in terms that can be interpreted as per cent such as 1/2 or 3/5), the CBCC codes it as an author's estimate by using Criterion 02, rather than Criterion 62. The latter criterion is thereby reserved for evaluations based on percentage calculated from actual measurements. For this reason, the eleven percentage ranges of Criterion 62 have been listed with Criterion 02, with their corresponding Field Y symbols. If an author does not make clear that his expression of percentage response is based on actual measurement, and there is no evidence in the data that it is not an estimate, use Criterion 02 rather than Criterion 62.

For coding of Field W when evaluation is coded according to Criterion 02, see the explanation in Division 4 for coding Field W when evaluation is coded according to Criterion 01. The same explanation applies to both Criteria.

6. "Inactivity" or "ineffectiveness", as an author's expression, may not be identical to "inactivity" or "ineffectiveness" as defined by Symbol 1 of Field Y with Criteria 01 and 02; special use of Symbol Q in Field W

It will be observed that Criterion 01 or 02 is used for positive data only when the author gives nothing other than his own statement of evaluation to use for a coding criterion, expressed verbally (Criterion 01) or by a scoring system (Criterion 02). (This is not to ignore the fact that Criterion 01 or 02 is to be used for any negative data, regardless of the way the author expresses it.)

Unfortunately, the interpretation by the coder of an author's evaluation is necessarily often speculative, since so much depends upon the individual author's concept of the meaning of the adjective or symbol he employs as that expression of evaluation.

In particular do the author's verbal expressions, "inactive" or "ineffective" (Criterion 01), or merely his symbol for "inactive" (Criterion 02), represent an ambiguity. Whereas to some investigators "inactive" may mean that no response was detected (i.e., true inactivity), others have used the expression to mean that a response was produced but it was at a level below that which the author considers of significance relative to the use for which the chemical was tested (i.e., actually active but below a practical active level). Likewise the term "ineffective" is used sometimes to convey the fact that there was no effect, in other words, no biological response, whereas another author may use it in the sense of "inefficiency", i.e., low effectiveness. Lacking any clue from the data, the coder has no choice but to code these authors' expressions with Symbol 1 of Field Y (unless correspondence with an author clarifies his use of the term "inactive" or "ineffective" as being actually either "no response" or "active but very low in effectiveness"). As a result, interpretation of the punched CBCC Symbol 1 in Field Y with Criterion 01 or 02 bears with it this identical ambiguity. (The author's expression, "no response", is more frequently intended literally and can be interpreted literally by the coder so that it can be more confidently coded with Symbol 1 of Field Y.)

Consider the fact that the CBCC codes all negative data (of which there are inevitably a great quantity, especially from screening-type tests), only by use of Criteria 01, 02, and 62; in other words, whether evaluation is or is not based on an author's verbal expression or scoring system, if it is negative, only Criterion 01, 02, or 62 is used. Compared to the frequency of this use of Criterion 01 (for any negative data, with Symbol 1 in Field Y), the frequency of use of Criterion 01 for coding an author's actual verbal evaluation or the coder's evaluation (Symbols 2 through 9, as well as Symbol 1) is low. Correspondingly, the problem discussed in the previous paragraph involving an author's verbal ambiguity involves only a very small percentage of the code lines representing negative data. Nevertheless, in selecting from the CBCC files all code lines in which the compound has been coded as producing no response, a certain unknown small percentage of those retrieved by Symbol 1 in Field Y would have to be considered as actually representing a positive response instead of no response, and to that extent the IBM punched card sort and the interpretation as "no response" would be inaccurate.

Inasmuch as there exists a convenient coding tool (Symbol Q of Field W) whose use can prevent the situation just described, in other words, the situation having a factor of unknown quantity and quality included in a set of retrieved negative data, the CBCC elects to use that means, even though it is perhaps contrary to the policy not to code implications the author has not specifically made. Thus, when the author expresses his evaluation merely as "inactive" or "ineffective" or merely with a symbol for "inactive" and there is no way of ascertaining whether there was actually "no response" or whether there was "positive response but very low effectiveness", code Field W with Symbol Q, rather than assume the author means to imply "no response" and code it with Symbol J (or K). (See Division 3 for the primary purpose of Symbol Q in Field W.)

In the case of expressions of degrees of positive activity, an inconsistency of meaning is recognized to exist between authors, in the same way as in the meaning for "inactivity" and "ineffectiveness". However, the ranking of positive activity (after having succeeded in the primary purpose of Fields X and Y--distinguishing fairly adequately, by code, "no response" from "positive response") is really the secondary purpose of the CBCC evaluation fields (as explained in the section on General Use). While it is important to be as accurate as possible in coding grades of positive activity, this grading can be only relative, at best. Therefore, the CBCC is satisfied to code the author's expressions of grades of positive activity literally, according to the explanations of Divisions 4 and 5.

7. Comparative expressions of evaluation used by the author (Criterion 01, 02, 03, and 04) are to be used for coding only when the data do not include the measurement of response

As indicated in Division 6, an investigator often interprets the intensity of the biological response in the light of the particular use for which the chemical was tested; his expression of evaluation reflects this relationship. To say this another way, an investigator often adapts his expression of evaluation to the general "biological field" concerned (e.g., the general field of weed control, as opposed to that of insect repellence, enzyme antagonism, or tuberculosis therapy, etc.).

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Columns 68; 69 and
70; and 71

The differences between certain biological fields which account for characteristic differences in general intensity of response are numerous; for example, the differences in control of the chemical's application (injection or topical application which is generally typical of medicinal administrations, as opposed to the agricultural spraying of the chemical outdoors over a plot or field of organisms where all weather factors may affect the deposit) or differences in the general type of organism (higher animals vs. higher plants), etc. Most commonly, the investigator takes into consideration the performance of other chemicals known to cause the particular response in the same general biological field for which the test compound has been applied and expresses an evaluation (e.g., "insignificant", "fair", "moderate", etc.) with this factor of comparison of chemicals in mind, though comparison might conceivably be made with a given test compound's effect in another organism, or by another route of administration, etc.

These interpretations by the investigator, of course, contribute much meaning to the results, for the reader of the author's journal article, report, or file data; comprehension of the significance of new data is always assisted by, or dependent upon, the use of the familiar as a frame of reference.

However, the variation in interpretation of results according to authors' special points of view represents a problem in coding test results so that all evaluation entries in the file will be on a reasonably comparable basis. In a sense, recording only the verbal evaluation made by an author represents coding by a separate classification scheme (i.e., the author's rather than the CBCC's) for which the criteria for evaluation are frequently obscure; similarly, every evaluation made by comparison to a standard compound represents coding by a unique classification scheme (according to the set of special attributes of the standard compound rather than the standards of the CBCC classification scheme for evaluations). The CBCC, therefore, prefers not to "index" by coding according to the author's classification concepts (Criteria 01 and 02), except when there is no alternative, nor to index by coding according to the special set of characteristics represented by some compound selected as a standard for comparison (Criteria 03 and 04), unless there is no alternative.

Whenever possible, it is preferred to derive an evaluation by making a correlation between the two basic measurements from the test coded, (1) intensity of response and (2) quantity of compound used to produce that intensity ("potency" of the compound, as defined in Division 8). The criteria which might conceivably be considered as permitting this are Criteria 20, 21, 22, 51, 52, 53, and 55. When this is for any reason impossible or impractical, the evaluation next in preference is by rating the test compound according to the measure of intensity of response--for example, killing time (Criterion 11), per cent increase in some normal function (Criterion 61 and 62), duration of action (Criterion 13), duration of action correlated with the incidence of that duration of action (Criterion 54), etc. In short, the CBCC coding of Field Y is intended to record uncritically and as accurately as possible the chemical's ability to cause the response or at least the intensity of response, while interpretation and comparisons are left for users of the files of coded data; any interpretations and comparisons made by the author should be included in the written abstract of the code line, however, to make them accessible to the interpreter of the coding in Field Y.

The symbol for "measure of response intensity" or the "potency value" is obtained by reference to fixed CBCC Field Y scales. (The term, "fixed", is meant to imply that, for any one criterion of Field X, the Field Y scale does not deviate according to the type or field of chemical-biological data, but data from all types of tests are graded on the scale.) Thus, these CBCC values coded in Field Y are not reduced to mere relative values by comparing them, for example, to the actions for other compounds (e.g., "the test compound causes only 50% of the response caused by compound X") or responses of other organisms (e.g., "the test organism responded only half as much as organism B") or the responses when administered by another route (e.g., "the response by intravascular injection was twice as great as by intramuscular injection" or "the response when sprayed on plants in the laboratory was six times as great as when sprayed on the exposed plant in the field"), etc. To make the evaluation expressions of these examples meaningful, there must be known the evaluations of responses caused by the factors to which comparisons are made--in other words, evaluation of the response caused by compound X, or caused in organism B, or caused by intramuscular injection, or by application to exposed plants in the field. It will be recognized that such comparative expressions of evaluation would require interpretation for which would be necessary a value that is not coded in the biology code line in which such a comparative evaluation would be coded (in the examples used here, the response of compound X is not coded, nor the response of organism B, nor of administration by intramuscular injection, nor of spraying of exposed field plants).

Unfortunately, an author frequently expresses his positive test results only in terms of a comparative evaluation so that the CBCC coder has available no measure of intensity of response or "potency" that can be used for coding. In this case, there is no recourse but to record the author's expression as well as possible and the person using the CBCC file has consequently always to interpret this author's expression in the light of whatever the author used as a factor for comparison.

Of these authors' evaluations, the least satisfactory for the CBCC is the author's use of mere verbal expressions (e.g., "ineffective", "low", "inactive", "high") or a simple scoring system; frequently, the author, in arriving at his verbal or scoring evaluation, has done so by relating it to the special character of the biological field involved and by comparing it to known actions under other conditions (known actions of other compounds, e.g.), but this is not necessarily always the case; it is an interpretation the CBCC would prefer delegating to the user of its files by supplying in Field Y only the measure of the response. Nevertheless, when nothing but an author's interpretation is available--his verbal expression or his scoring evaluation, the only coding possible is by Criterion 01 or 02 and the person subsequently using the CBCC files must make what interpretation he can of the coding of this author's evaluation by studying the written abstract (as well as the coding) of the biology code line.

An author's comparative expression of test results is frequently by comparison to a standard compound. Thus, the coder may be supplied with nothing but this comparative expression (e.g., "50% of the response of compound X" or "the test compound had to be administered in twice the amount of Compound X to produce the peak action of Compound X"); in other words, the author may not reveal what was the measure of response of the test compound which, when compared to this standard compound, gave the comparative evaluations ("50%" or "twice as much"). In this case also, the coder has no choice but to code the comparative expression supplied by the author and the user of the CBCC files must interpret the expression as best he can by studying the CBCC biology code line and by learning what he can of the response to the standard compound. Criteria 03 and 04 have been included in Field X, with a fixed scale for coding Field Y, for those comparative expressions of evaluation. They are described thoroughly in Division 9.

8. Rating of the biological activity of chemicals on the basis of the QUANTITY of the chemical needed for a GIVEN INTENSITY of biological response (POTENCY)

In these descriptions of evaluation criteria, the term "potency" is used to describe a test compound's capacity for causing a biological response. Thus, a compound which did not cause a particular response regardless of the quantity administered would be described as having zero potency for causing that response; the data would be negative. When the test compound does produce the response, however, its potency is measured by two factors: intensity of response and minimum dose needed to produce that intensity of response. The smaller the quantity needed to produce a given intensity of response, or the greater the response intensity to a given quantity, the higher is the compound's potency. The following sections, A and B, discuss and define "intensity of response", the consideration of which is important before the concept of "potency" is further discussed.

A. Intensity of response in a SINGLE INDIVIDUAL ORGANISM

Intensity of response is most easily understood as a variable in a single individual organism, varying with the dose size administered, up to a point of maximum degree to which the test compound is capable of inducing the response or to the maximum degree to which the organism is capable of making the response.

Not all specific responses of Field T, as they occur in the individual organism, lend themselves to precise measurement in terms of "intensity". In particular, attention is called to the responses whose definitions exclude any intensity variation in the individual organism: death (toxicity, Symbols 11, 111, and 112 of Field T-2) or cure (Symbol 172), for example. Also, when no definite terminal or maximal intensity can be fixed for a response which does vary in intensity, expression of degree of intensity is difficult or impossible; many Field T-2 responses, when caused by the test compound rather than altered by the test compound, exemplify this: the locally toxic responses (symbol series 113-) when caused by the test compound, or production of edema, thrombosis, fibrosis, neoplasms, pain, hyperpnea, etc. The intensity of these can not be expressed as a per

cent increase over a normal condition, since these are abnormal conditions induced by the compound; neither can the intensity be expressed as a per cent of a maximum (100%) edema, pain, hyperpnea, etc., because fixing a maximum for such responses is in most cases impossible. Therefore, for such responses as death, edema, thrombosis, etc., induced by the test compound, about the only practical way of making a comparative evaluation of test compounds' potencies is by comparing threshold doses of the compounds (i.e., ignoring the intensities of edema, hyperpnea, etc.), using Criterion 20. (If intensity of such a response is to be coded, it can only be by terms such as "mild", "fair", "severe", etc., Criterion 01.)

However, if the action of the test compound causes an increase or decrease of a normal physiological function or an increase or decrease of normal size, weight, or growth of the organism or anatomical structure, the intensity of response can be measured and expressed as the per cent increase (0% through, or greater than, 100%) or per cent decrease (0% through 100%). Likewise, if the response has a known terminal point (such as the chemical alterations indicated by the FE-- symbol series of Field T-2, or tumor regression, or tissue regeneration and wound healing, relief from a pathology, degenerations, inhibition of specific actions of secondary compound, etc.), the intensity of response to the test compound can be measured and expressed as the per cent of that terminal intensity (0% through 100%).

Thus, in an individual organism, the intensity of response can frequently be expressed in definite terms of percentage of response possible or percentage of increase or decrease and this might be correlated with the minimum quantity of test compound producing that given intensity of response. If doses of increasing size were given to the organism in a series of tests and the response in each succeeding test was shown to increase in intensity corresponding to the increase in dose size, plotting the doses against the corresponding response intensities would result in a characteristic curve which theoretically could be compared to similar curves plotted for other test compounds and to which could be assigned a code evaluation. Note that the CBCC has devised no special mechanism (i.e., a standard graph or grid) for making this evaluation by comparing these dosage-response intensity curves and therefore no criterion in Field X derives an evaluation thereby. However, evaluations are derived by comparing test compounds by one end of this dose-response intensity curve (the threshold end), in using Criterion 20 with "death" or other all-or-none response. In this case, the degree of response intensity can be ignored so that plotting of the threshold dose-response could be conceived as restricted to the abscissa (the dosage scale); thus, CBCC evaluation of the potency of compounds according to the threshold of response is adequate by using only the dosage scale. Evaluations could be derived (though the CBCC has established no criterion for doing so) by comparing all compounds by the other end of the dosage-response intensity curve. This latter could conceivably be done by establishing a special graph on which the ordinate would be an arithmetic scale of 0-100% response intensity, divided into areas representing code evaluations (as in the case of the Log-Probit Grid, described in Division 24, whose ordinate is a scale of 0-100% of organisms responding). On this special standard reference graph could be plotted the point of maximum intensity of response of which the test compound is capable (at any dose) vs. the minimum dose causing that response.

Actually, by present CBCC procedures, potency of a compound for a given biological action is a quality that the interpreter of the code line can judge only by consulting both the dosage fields (M, N, O, and P) and the fields recording response intensity (U, X, and Y); the two factors are never correlated to derive a Field Y evaluation coordinate, in the case of a response of the individual.

B. Intensity of response of the individual organism considered as a VARIABLE OF DIFFERENT INDIVIDUALS; INCIDENCE of a given intensity of individual response IN A GROUP OF INDIVIDUALS; the expression "intensity of response" when applied to a group of individuals, is the DEGREE OF INCIDENCE of specified intensity of individual response.

In addition to measuring intensity of response in an individual organism (section A above), a third factor is often introduced, that of variation in individuals. By fixing this intensity of response in the individual organisms as a point of reference, a number of individuals can be tested to determine the percentage of individuals that will respond at that given intensity of individual response at any given quantity of test compound. Commonly, the intensity of individual response is fixed as being "threshold" response, or it is a response such as death which has no variation in intensity in the individual, or fixed by definition to be "effective dose", etc. The potency of the test compound in this case can be defined as a a measure of two factors as follows: the percentage of organisms the compound can affect to that given intensity of individual response (e.g., threshold, maximum intensity, or death) and the quantity of the chemical needed to affect that number of organisms to that given point. The test compound that can cause a given intensity of response in a large number of organisms when administered in small quantity has a higher potency than other compounds that cause the same intensity of response in a smaller number of organisms or when administered in larger quantity.

In the case of either of the potency definitions ([A] quantity of compound vs. per cent intensity of response in the individual organism and [B] quantity of compound vs. cumulative per cent of organisms responding at a given intensity), the plotting of the two factors on graph paper results in curves characteristic for any given test compound and any given response.

For the second of these (quantity of test compound vs. cumulative per cent of organisms responding), a special type of graph paper has been used, designed for correlating the two factors involved, for any compound and any specific response in any organism. (See the description of the CBCC Log-Probit Grid, Division 24.) The potency of the test compound for any specific action is indicated by the position of the points plotted on that Grid, relative to the positions of points plotted for other compounds.

9. Criteria 03 and 04; comparison of the test compound to a standard compound by comparing the two levels of response produced by the two compounds when applied at the same dose level (Criterion 03) or by comparing the dose levels, of the two compounds, needed to produce the same level of response (Criterion 04)

The discussion of Division 7 has explained why Criteria 03 and 04, like Criteria 01 and 02, are used for coding intensity of positive response only when it is impossible to use other criteria, for lack of proper data. It is preferable to relate the degree of biological response to fixed CBCC scales, rather than to other factors such as responses of other compounds.

It is not the intention here to imply that evaluations based on comparison to standard compounds are always inconvenient except when it would add unnecessary complexity to subsequent retrieval and interpretation. In a limited coding program, restricted to data from only a few test procedures, when many or all evaluations are based on one or a few standard compounds with which the persons subsequently using the file would be entirely familiar, Criteria 03 and 04 might well be preferred to any other.

Consider a test compound which caused nearly the same intensity of response as a standard compound (84% compared to 87%--i.e., both caused approximately 85% response) when administered at the same dose level as the standard. The quotient of comparison would be approximately 1.0, coded by Symbol 5 in Field Y (Criterion 03); the code line for the standard compound would be coded with Symbol 8 in Field Y (Criterion 62). Here, the degree of response to the test compound is actually quite high (equivalent to the high evaluation for the standard compound indicated by Symbol 8), but it is not revealed by the evaluation coding in Field Y except by reference to (i.e., interpretation by) the evaluation of the standard compound's performance by Criterion 62, recorded only on another punched card. Consider a second example in which the test compound and a standard compound both caused 50% response, but the quantity of the standard compound needed to produce that response was only one fourth that of the test compound. I.e., the standard is the more "potent" of the two chemicals.

The coding of 0.25, the relative potency of the test compound, would be by Symbol 3 of Field Y, using Criterion 04. In this case, however, the coding in Field Y does not reflect the intensity of response of either the test compound or standard and reference must be made to coding of the test for activity of a standard compound (on another punched card and code sheet) to learn the intensity of its action. It is to avoid this complication, when retrieving and interpreting coded data, that Criteria 03 and 04 should be used by the CBCC coder only when the actual measure of response of the test compound is unavailable and only the quotient for comparison or a verbal comparison are given by the author.

When the author presents evaluations in terms of comparison to another compound tested concurrently and by the identical method, this comparison should always be recorded in the written abstract, but it should not be coded (using Criterion 03 or 04) unless the author does not give the measure of intensity of response (which could be coded by another criterion) and gives only the quotient of comparison with the standard. Exceptions might be made to this, for CBCC coding, for screening-type tests made on a large number of test compounds (using a constant test procedure for a given biological response) with results expressed in terms of comparison to one standard compound, itself thoroughly tested and coded.

When it is necessary to use Criterion 03 or 04, note that the result of the test which was performed to evaluate the standard compound's activity must always be coded, in order that these data may be available for comparison with evaluation of compounds tested by the identical method and conditions.

The conversion of actual measurement of response or potency into comparative values (when Criterion 03 or 04 is used) makes coding of Field Y unique. The scale of comparative values has been broken into five ranges and assigned symbols 1, 3, 5, 7, and 9. As has been pointed out, however, this coding has no exact meaning without the coding of the standard compound to which comparison is made, except that it is generally assumed that a compound to which comparison is made has caused a positive response to some more or less satisfactory degree and that the test compound is more or less potent than the standard compound as indicated by the coding in Field Y.

In addition to numerical comparative expressions (i.e., numerical quotients of comparison between a test compound and a standard compound), an author occasionally expresses a general comparison verbally--"more than", "less than", or "equal to" the response to, or the potency of, a standard compound. Symbols 4, 5, and 6 have been assigned to those general verbal comparisons for Field Y when Criterion 03 or 04 are used.

The following are observations on code entries of Field W, when using either Criterion 03 or 04 in Field X. When Criterion 03 or 04 is used, it may ordinarily be assumed that the standard compound has been tested so thoroughly that dose sizes and response intensities to which the test compound is compared are minimum doses causing the intensity of response caused by the standard. When the test compound is known to have produced the maximum response intensity of which the compound is capable, the coding of Field W depends on the dose-response relationship; if the author indicates that the dose of test compound used in his calculations has been demonstrated to be the minimum dose needed to produce maximum response, code Field W with Symbol Ø; if the dose of test compound producing maximum response is not demonstrated to be the minimum dose needed to produce that maximum response, code Field W with Symbol M or N. Field W would be coded with Symbol L or P if the test compound were stated to have produced an intensity of response which is not known to be the maximum intensity of which the compound is capable. (Refer to the section on General Use which distinguishes in more detail the meanings of Symbols L, M, N, Ø, and P.)

10. Criteria 10, 11, 12, and 13; rating of the compound's ability to produce the response, based on time values

Criteria 10, 11, 12, and 13 are examples of criteria for which there are scales for units of measure of the response; in this case, the scales are in terms of units of time and they (or Criteria 54, 57, 58, and 59, to be described in their turn) are used whenever the test results have been measured in such units. However, because the scale for any one of these criteria is not a fixed scale, but a scale that expands or contracts in scope, to accommodate to the type of specific response produced, the rating of positive response which these criteria afford in Field Y is of little more significance than rating of positive response in Field Y by Criteria 01, 02, 03, and 04, as the remaining paragraphs of this division will explain.

The effectiveness of the test compound (Field Y) in some data (those measuring the speed of response, such as the time to a specific action other than death and those coding killing time) represents the reverse of the time value by which the response was measured; the greater the speed (i.e., the shorter the time), the greater is the degree of response. Therefore, a special field (Field U) was established for recording the actual time measured in the test, the evaluation of that time value being given interpretation in Field Y, according to whether evaluation is based on the time value or on the reciprocal of the time value.

Each of the four time values (i.e., Criteria 10, 11, 12, and 13) on which are based Field Y evaluation ratings is discussed thoroughly in the section on Specific Directions and Explanations for Field U and reference should be made to that section.

From the preceding, it should be understood that the scale used for Field Y symbols rating the response intensity, is actually the Field U scale, with the exception that it becomes reversed in the case of Criterion 10 or 11:

Criteria 10 and 11:		Criteria 12 and 13:
Field U Scale	Field Y Scale	Field U and Field Y (identical scale)
1	9	1
2	8	2
3	7	3
4	6	4
5	5	5
6	4	6
7	3	7
8	2	8
9	1	9

The reversal of scales for Criteria 10 and 11 is due to the fact that a short time to the beginning of a specific response other than death or a short killing time is indicative of a high activity rating for the test compound and vice versa.

If it is observed that the scale of symbols for Field Y is identical to the scale of symbols for Field U (even if the values are reversed as in the case of Criterion 10 or 11), it will be observed also that the Field Y scale for Criteria 10, 11, 12, and 13 is not fixed in the same way as the scale is fixed for rating responses by percentage values (Criterion 62), for example. Instead, the Field Y scale shifts according to whichever of the several Field U scales is used. In the discussion of Field U (and Field P), the coder's choice of a scale for coding in Field U (and Field P) is explained; in essence, this choice is largely a matter of elimination, i.e., dismissing from use any scales on which the time value to be coded would be coded with least meaning. (For example, time periods of 2, 2-1/2, and 3 hours would scarcely be meaningful if coded by Scale 1, 2, or 3 of Field U, nor would 1, 2, 3, and 6 minutes be meaningful if coded by Scale 5, 6, 7, 8, or 9 of Field U.) Actually, an examination of the scales of Field U will reveal that they represent a sequence of expanding time periods; i.e., each succeeding scale covers a greater expanse of time and the ranges within that scale are correspondingly expanded over the ranges of the preceding scale. As illustrated by the examples above, these specific responses (other than death) involving brief time periods can be coded significantly only by using a scale whose ranges are narrow enough to show appropriate discrimination between responses. On the other hand, there are specific responses other than death which involve comparatively long periods and these can be coded significantly only by using a scale covering such large expanses of time. Thus, Field U scales provide an automatic accommodation to the general size of the time period or periods involved; to the extent that this size of the time period is typical of certain specific responses other than death, Field U can be said to accommodate to the specific response coded in Field T (or to accommodate to the "biological field of study"). In turn, to the extent that Field U permits this accommodation by its scales, Field Y will also reflect the accommodation, by the fact that whatever scale is used in Field U becomes the scale for evaluation of Field Y. Note that the choice of scales in Field U can not be always exact and consistent; adjacent scales are not so different that one might not frequently be used as well as the other. (For example, the time value, 2 days, might be coded by any of scales 6, 7, or 8, according to whichever seems best in the light of what is known about the specific response or the

particular "biological field of study", though it would hardly be coded by Scales 1, 2, or 3.) Thus, the CBCC rating in Field Y can not be regarded as exact; in the example just cited, 2 days might be coded in Field Y (as well as in Column 66 of Field U) with any of Symbols 7, 4, or 2, according to which of Scales 6, 7, or 8 the coder elects to use, according to his best judgment, in Field U.

For the reasons just explained, in retrieving data from the CBCC file, none of the Field Y values derived by the time criteria should be regarded as being of high critical significance as a rating of the test compound's ability to produce the response. Of the coding in Fields U, X, and Y, Field X defines the time period the author has measured, Field U expresses fairly adequately the measure of that time, while Field Y can only attempt to place a speculative rating on that measure according to the judgment of the coder relative to the appropriateness of the scale used in Field U. The CBCC has persisted in making these ratings of positive response according to time measurements, on the premise that its coders' judgments in rating were of more significance than no rating at all of the positive activity and that theoretically the rating coded in Field Y has some significance by having been derived through accommodation to the specific response. Nevertheless, the person using the CBCC files should always regard the Field Y ratings made with Criteria 10, 11, 12, and 13 as being only suggestive ratings and his study of the coded results of the test should be concentrated on the definite information coded in Fields T and U.

The alternative to the provisions made by Field U would be the construction of a single, fixed scale for Field U by which time values from all types or fields of chemical-biological data would be rated. This, of course, would result in certain types of data (those typically involving only brief time values or those typically involving only very long periods) all being coded by one or a few symbols at one end of the evaluation scale (all being coded as being highly active or all as having very little activity). It is suggested that the selection of only one of these two alternatives may be inadequate and that, ideally, both evaluations are significant and provision for both should have been made by the CBCC, the evaluation according to a single time scale being made for broad comparisons disregarding the type of biological response involved (requiring subsequent reference to the coding in Field T to discern what type of action was involved and evaluated in the test), as well as a second evaluation according to the variable scale of Field U which would be an evaluation scaled to the type of biological response (an evaluation to be used when studying an assortment of assembled coded data on biological response of a given type).

If the response which would have been measured in time values did not occur, Field X would be coded with Criterion 01 with Symbol 1 in Field Y and Field W coded with Symbol J or K, according to the character of the dose level, as explained in the section on General Use and in the Code. Therefore, when Criterion 10, 11, 12, or 13 is coded in Field X, the data must be positive. Field W would be coded according to whether tests had demonstrated the maximum speed of action or maximum duration of action or maximum increase in survival and whether the dose administered had been demonstrated to be the minimum needed to cause the observed measure of response. The use of Symbols L, M, N, Ø, and P in Field W for this information is also described in the section on General Use and in the Code.

11. Criteria 14, 15, and 16; rating of intensity of the response according to therapeutic and chemotherapeutic indexes

A common means of expressing a compound's value as a therapeutic agent is by relating its beneficial "potency" (i.e., the minimum quantity needed to cause the desired therapeutic result) to its harmful "potency" (i.e., the lowest quantity needed to kill the organism in its uninfected normal state or the highest quantity that will not kill the organism). The ratio thus established provides a comparative value for a compound, which can be rated according to a fixed scale; in other words, the value indexes test compounds according to their therapeutic values related to their margins of safety.

While such an index value is significant for purposes of comparing compounds, the CBCC prefers coding the factors of the ratio independently, a biology code line for the curative action and the minimum dose producing it, and a biology code line for the lethal action and the minimum dose producing death or the maximum dose that does not produce death.

However, an author occasionally does not provide the coder with anything but the index itself (i.e., neither the minimum curative dose nor the lethal dose which were used to calculate the index). In this case, the coder has no choice but to code in Field X the terms of the author and for this

eventuality, Criteria 14, 15, and 16 are provided. Since these criteria measure the compound's value in curing or producing relief from a disease and can be used only when such action has been demonstrated, it follows that when those criteria are used, the action coded in Field T is necessarily that of curing the organism of, or producing some degree of relief from, the disease; thus, when Criterion 14, 15, or 16 is used, the biology code line records the details of the therapeutic test; Criteria 14, 15, and 16 are never used to evaluate the compound's ability to kill the diseased host.

Ordinarily, when the author gives the minimum lethal dose as well as the index, the therapeutic dose level can be calculated for Fields M and/or N and the use of Criterion 14, 15, and 16 can be avoided. When the coder must use Criterion 14, 15, or 16, it is because he has only the calculated index and can not determine the therapeutic dose; therefore, when Criterion 14, 15, or 16 is used, Fields M and N can not be coded.

Because of the usefulness of the index values in comparing chemicals on their therapeutic merits, it is conceivable that under certain circumstances, it would be worth the time and expense to construct biology code lines with the therapeutic index or the chemotherapeutic index coded in Fields X and Y, in addition to constructing the two code lines evaluated by the therapeutic dose level and by the lethal level, when the latter two values are known. The CBCC has actually constructed such code lines, using Criteria 14, 15, or 16, in addition to constructing lines evaluated by the therapeutic dose level and by the lethal level, in coding data from certain large screening projects, when many chemicals have been tested identically, resulting in many chemotherapeutic indexes of considerable value because they referred to the same treated condition.

Ordinarily, data which evaluate a test compound by therapeutic or chemotherapeutic indexes are known to be positive data and if Criterion 14, 15, or 16 is used, Field W should be coded with Symbol Ø, since the therapeutic dose is claimed by definition to have been determined to be the minimum needed to cause the desired (maximum) therapeutic response.

12. Criterion 17; rodent repellency index

The quality of a compound which enables an organism to sense the compound and be repelled by it or be attracted to it can be measured by the percentage of a group of organisms repelled or attracted or by the quantity of the compound needed to repel or attract.

In testing chemicals for their repellent/attractant quality for rats, a special method has been devised which consists basically of applying the test compound to the food of laboratory rats at a fixed dose level and subsequently comparing the consumption of that treated food to the consumption of untreated food offered concurrently to the rats, any marked preference on the part of the rats being taken as a measure of the repellent/attractant quality of the compound.

Results from this test procedure are expressed by a "repellency index" which is the result of a standard calculation, the formula for which is as follows:

$$K = 100 - 1/100\ W\ (8T_1+4T_2+2T_3+T_4)\ (U_1+U_2+2U_3+4U_4+8X)$$

In this formula, W represents the body weight of the animal in kilograms, T_1, T_2, T_3, and T_4 represent the daily consumption of the treated food (the standard duration of the experiment is 4 days), U_1, U_2, U_3, and U_4 represent the daily consumption of the untreated food, and X represents any untreated food remaining at the end of the experimental period.

Inasmuch as hundreds of compounds have been given this particular test and rated according to the calculation above (using the fixed dose of 2% in the food), the CBCC has assigned a unique Field X symbol to the repellency index, Symbol 17. On advice from investigators using the test, relative to the significance of the repellency index, a Field Y rating scale has been established using Symbols 1, 3, 5, 7, and 9. An index value less than 80 is regarded as being indicative of a repellency too low to be given practical consideration in the investigator's opinion and subsequently it is coded in Field Y with Symbol 1; this does not always mean that the test compound proved totally nonrepellent. Actually, evaluation by Criterion 17 represents a special "Author's Evaluation" (Criterion 01) and the criticisms made of Criterion 01 (see Divisions 4, 6, 7, and 8) would apply equally to Criterion 17, except that, by Criterion 17, the basis for the author's statement (i.e., the author's criterion) is specified by

definition of Criterion 17. The evaluations made by Criterion 17, nevertheless, are essentially only meaningful when studying coded information on compounds tested by this method. (A CBCC code evaluation based solely on a percentage difference between amounts of treated and untreated food consumed might have been preferable, using Criteria 61 and 62 or a special criterion, leaving interpretation of that differential, as to its significance as a repellent, to an entry in the written abstract accompanying the coding or providing a second coding area for evaluation according to the author's concepts.)

The person using the coded files for purposes of comparative repellency studies will need to refer to the Biology Code Sheets in the case of those compounds coded with Criterion 17 in Field X with Symbol 1 in Field Y, in order to study the actual comparative consumption of treated food. For this reason, the coder should always include in the written abstract of the code line, in addition to the actual index, the measurements made from the test, if given by the author--i.e., the amount of treated food consumed per day, the amount of untreated food consumed per day, the weight of the animal, the amount of the test compound consumed, etc.

If the rats exhibited no preference (when as much treated food was consumed as untreated food), indicating actual inactivity of the compound as a repellent, Criterion 01 should be used with Symbol 1 in Field Y, and Field W should be coded with Symbol K (or with Symbol J if the dose of 2% were stated to be the maximum tolerated).

When coding repellency data from tests using the standard dose of 2%, Field W should be coded with Symbol L (unless the 2% level should have been demonstrated to be the maximum tolerated dose, when Symbol M should be used, or unless it should have been demonstrated by additional testing to be the minimum dose causing the greatest response, when Symbol Ø should be used), since the single dose level administered by the standard testing procedure does not demonstrate whether smaller doses would cause the same or less repellency.

13. Criterion 18 (Tolerance Increase) and Criterion 19 (Sensitivity Increase)

A. Criterion 18:

This criterion is for expressing the degree to which an individual organism has adjusted to a test compound over a period of time so that the original sensitivity of the organism to the compound is diminished; i.e., the organism's tolerance for the test compound has increased. Coding of this increase of tolerance is discussed in Fields M and N (Division 11A of the Specific Directions and Explanations of Fields M and N), but the provision made for it is reviewed here briefly.

For measurement of tolerance increase in the test organism, the intensity of toxic response, in the case of Criterion 18, is fixed by definition at the same point as with Criterion 21. This intensity is defined for Criterion 21 as a negative level: i.e., the organism's unresponsiveness which immediately precedes the organism's response as the dose size is increased. (See Division 15.) Therefore, like Criterion 21, the potency of a drug for causing this toxic effect is expressed adequately in terms of the dose size.

The reduction of sensitivity in the individual is expressed sometimes as "tolerance development" rather than "tolerance increase", or as a decrease in sensitivity of the organism, or as an "increase in resistance to the test compound" or as "increase in, or production of, refractoriness" to the compound. Regardless of the expression used, the phenomenon is demonstrated only by determining the minimum initial dose level that is toxic to the individual organism and, after an appropriate interval, the minimal final dose level that is toxic to the same individual. Increased tolerance is demonstrated when the final tolerated dose level is significantly greater than the initial tolerated dose level. Inasmuch as this phenomenon occurs in the individual organism, the toxic effect is some toxic symptom other than death, because death in the individual precludes determining subsequent tolerated quantities of the test compound.

As was suggested by the first statement of this discussion of Criterion 18, the evaluation expressed by the criterion may be regarded as an evaluation of the test organism's ability to adjust to the test compound, rather than an evaluation of any specific action of the test compound. Only by stretching the concept of the "specific action" can tolerance to the test compound be considered as

an action of the compound (e.g., "the test compound, by its presence, causes the test organism to alter so that it can tolerate greater doses of the test compound"). If Criterion 18 is used in Field X, Field T-2 would necessarily be coded with a symbol of the 51-- series (Symbol 512) rather than with a symbol for any toxic response. However, a description, by the author, of the test compound's specific toxic action would be expected with data describing tolerance increase and this should be coded by constructing another biology code line, with Field T-2 coded with the symbol for the toxic response and an appropriate Criterion other than Criterion 18 coded in Field X.

Criterion 18 is intended for use when the author states the two tolerated dose levels which are separated by a time interval. The ratio of the two doses provides a value to be fitted on a fixed scale of the Code, from which scale is derived a code symbol. It expresses the comparative ability of the test compound for becoming tolerated by the test organism (as compared to other toxic compounds) or, in terms of the test organism, it expresses the comparative ability of the test organism to adjust to the test compound (as compared to other test organisms' abilities to adjust similarly to the compound).

In the individual test organism, this specific action is measured solely by the difference between before-and-after dosage levels. This is the intensity to which the "action" occurs and the dose level producing the tolerance is not considered a part of the expression of "potency" for increasing the tolerance. (See Fields M and N, Specific Directions and Explanations, Division 11A, for a more complete discussion of coding procedures for tolerance increase.)

No criterion is proposed here for evaluating tolerance increase according to the incidence of a given intensity of tolerance increase in a group of individuals. Criterion 62 might be used to express the fact that, of a group of individuals, a given percentage demonstrated tolerance increase of unspecified degree.

B. Criterion 19:

This criterion is for evaluation of the test compound's becoming "decreasingly tolerated by the individual organism". I.e., it evaluates the individual's increased sensitivity to the test compound, when the author has determined the initial threshold dose and, after an interval, the final threshold dose or the initial maximum tolerated dose and the final maximum tolerated dose. When these final doses (final threshold or final maximum tolerated) are significantly lower than the initial doses, the measurement is interpreted as evidence of increased sensitivity.

As with Criterion 18, a code evaluation for Field Y is derived by the ratio of the two doses (initial and final), fitted to a fixed scale.

Neither Criterion 18 nor Criterion 19 have as yet actually been needed by the CBCC. They are suggested here, however, as a means of evaluation when Field T is coded with "increase of tolerance" (Field T-1, Symbol 1; Field T-2, Symbol 512) or with "increase of sensitivity" (i.e., "decrease of tolerance", Field T-1, Symbol 2; Field T-2, Symbol 512) and when the values needed for the respective ratios have been given by the author.

14. Criterion 20; threshold dose or minimum effective dose; dose just larger than the maximum dose which does not produce the specific response

Criterion 20 might conceivably be regarded as a criterion relating intensity of response and size of dose needed to produce that intensity, to provide a coordinate evaluation that would be an expression of the compound's potency. This is suggested by the criterion's definition by which one of the two factors, response intensity, might be regarded as being fixed as a standard intensity, the threshold. This would require making the assumption that any given response in a given test organism is apt to occur at a standard threshold intensity, regardless of the compound inducing the response. However, since it might well be argued that a response may vary widely in initial intensity according to test compounds' characters and it might further be argued that the evaluation of a test compound should include consideration of this initial intensity of response as well as the dose size initiating the response, evaluations made by Criterion 20 should probably be regarded as no more an expression of potency (dose-intensity coordinate) than Criterion 10 or 62, for example. In the case of "death" in the individual, any other all-or-none response, or "death" defined to represent 100% kill of a population (see the second paragraph following), when threshold intensity is by definition unvarying, Criterion 20 can legitimately be regarded as giving a Field Y evaluation representing comparative "potency".

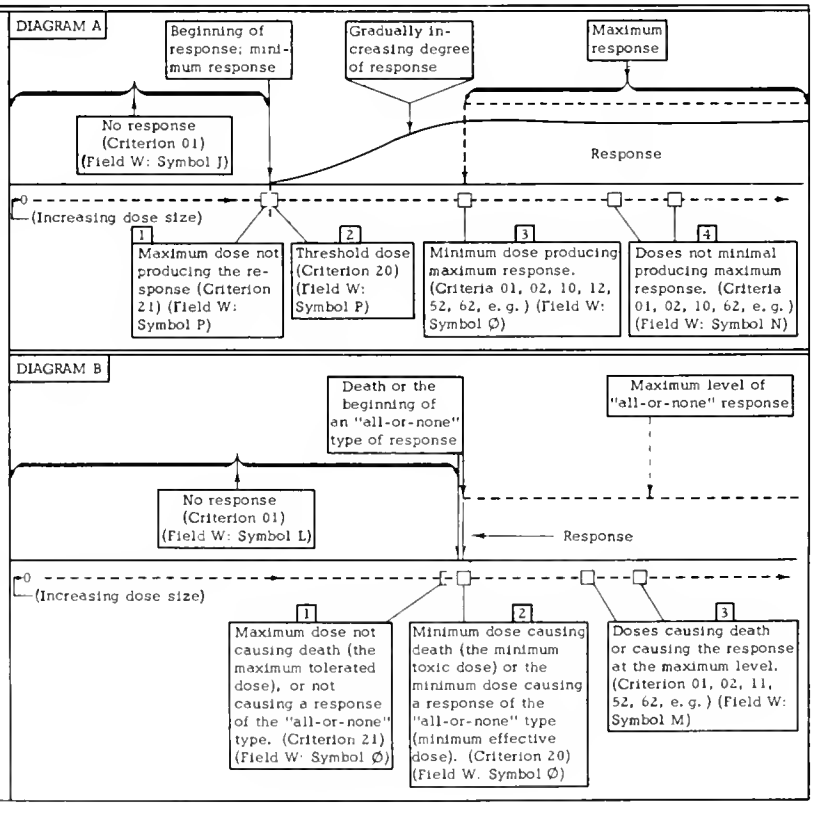
In any case, the relative merits of test compounds, for any given biological response, are expressed by this criterion solely on the basis of the relative size of the dose needed to produce this standard response level. The especially desirable quality of the criterion and the rating it gives is due to the fact that the level of response selected as a standard is a significant and experimentally practical one, the first appearance of the given response (implying the lowest level of the response) as the dose size is increased progressively from a level that did not cause the response. This is referred to in most cases as the threshold of response and the dose level producing it is referred to as the threshold dose.

Some responses are essentially "all-or-none" (i.e., the response either does not occur or, when it is produced by a dose of sufficient size, it occurs at its maximum intensity); the most absolute and conspicuous example of this is the phenomenon of death. When death is the biological response of an individual organism, the word "threshold" is scarcely an appropriate term, since it carries the implication that the response's initial appearance can be followed by a greater degree of response and this, in the case of death of the individual and any other "all-or-none" type of response, is impossible. Nevertheless, frequently a laboratory test determines the lowest dose which causes death or some other "all-or-none" response. Criterion 20 must be used for rating the compound according to the minimum quantity (or maximum dilution or minimum duration of administration) needed to produce death or any response which is, like death, "all-or-none". This is conveniently referred to as the "minimum effective dose", an expression which at least has the virtue of avoiding the definite implication that the response might occur to a greater degree if a greater quantity of compound were administered.

Avoiding the implications of the term "threshold", as pointed out above, and the ambiguities of the word "effective" (see the ninth and subsequent paragraphs of this division), Criterion 20 can best be defined as the criterion which bases an evaluation on the dose which is just greater than the highest dose which does not produce the response coded in Field T. The following diagrams illustrate the use of Criterion 20, as well as of Criterion 21, relative to responses as they occur in the individual organism. (I.e., the diagrams are only intended to illustrate responses of one individual of the species tested, not of a population or group of individuals of the species tested.)

Diagram A is concerned with any specific response that exhibits graduation of degree below maximum. The horizontal dose line does not represent a continuous application, but merely increasing size of dose; any single point on the dose line represents a single dose of determined size. Neither does the response line represent a single response in an organism, but any single point represents the level to which the response would rise corresponding to the size of any single dose on the dose line.

Diagram B is concerned with death as the specific response or with a response that exhibits no graduation of degree below maximum (an "all-or-none" type of response). The dose line and the response line are as described above for Diagram A.



In determining the threshold dose for a specific action, a single individual organism can conceivably be used, administering successively larger doses, separated by appropriate intervals, till the threshold point is reached. (These sub-threshold doses need not be written on the Code Sheet and they must not be coded; only the threshold dose should be coded in Fields M, N, and P.) The more common test procedure, however, involves administering each of the different sized test doses to different individuals, in which case the smallest dose producing the response to any degree in that group of individuals is interpreted as the threshold dose. (This does not concern determination of the percentage of individuals responding to that lowest dose. The determination of percentage of individuals whose threshold response is with a given dose is a more infrequent and critical test discussed later in the division.)

Since Criterion 20 places a rating on the compound according to only the size of the dose, as explained in the first paragraph of this division, the rating coded in Field Y is determined by reference to the coding of the threshold dose in Field M, N, or P. (Note the following paragraph.) The size of the dose in the dosage field is indicated by the coding in Column 48 of Field N (or in Column 46 of Field M or Column 51 of Field P). This is merely transferred to Field Y as the rating for comparison with other compounds. A low figure used as a symbol in Field M, N, or P indicates a low dosage; a low figure used as a symbol in Field Y indicates a low response; since a low threshold dose indicates a high potency, it is necessary to use in Field Y the reciprocal of the figure used in Field M, N, or P, as follows:

Field M, N, or P: coding in Col. 46, 48, or 51	Field Y: Coding in Col. 71
1	9
2	8
3	7
4	6
5	5
6	4
7	3
8	2
9	1

The threshold dose will usually be in Field N, because it is most frequently determined and expressed as the actual quantity of pure compound, or equivalent, administered in a single dose. For purposes of comparison of compounds' threshold doses, this quantity given as a single dose to produce threshold response (Field N) is the preferable one, though in certain types of therapy which are necessarily or typically by a series of administrations, the threshold dose size might be defined best in terms of Field P or Field M. If the threshold dose evaluation is based on "duration of administration" (Field P) or "concentration" (Field M), the coder should always clearly indicate it in the written abstract for Field Y.

The threshold dose is probably never more than an approximation even under the most exacting conditions, due to differences between test organism individuals and variables in conditions prevailing at different determinations of the dose. Therefore, for therapeutic drugs, an effort might be made to determine the variation in thresholds of a given response in several individuals. (For example, "in 10% of the organisms, the threshold dose was 1 mg; in 20%, it was 1.5 mg; in 50%, it was 5 mg; and in 20%, it was 10 mg".) In this event, the CBCC plots the data on the Grid (double coding the dosage field with the extremities of the range of threshold doses corresponding to the range represented by the evaluation symbol coded in Field Y), as explained in Division 8 (Subdivision B) and Division 24. This is in lieu of selecting only one of the threshold determinations (of the range of thresholds demonstrated in the group of individuals) and giving it a Field Y rating according to that selected threshold dose, or of constructing a separate code line for each. The procedure is possible by regarding one of the three factors involved (individual intensity of response vs. dose size vs. percent of organisms)--the intensity of response of the single individual of the species tested--to be non-variable at threshold level; the remaining two factors can be plotted as variables to derive an evaluation correlate. Note that when plotting a dose size against a percent of organisms responding, CRITERION 20 CAN NOT BE USED, but only Criterion 51, 52, or 53.

If the author expresses a threshold dose only as a range (e. g., "the threshold response in the single individual was with 20-30 mg" or "the threshold response in 50% of the organisms tested was with 20-30 mg"), the CBCC codes that threshold dose in the dosage fields as being an average of the extremities of the range and derives a Field Y rating directly from the coding of the dosage field (Criterion 20) or through the Grid (Criterion 51, 52, or 53).

A problem of definition accompanies Field Y ratings expressed as "minimum effective dose". The problem derives from the ambiguity of the word "effective". Attention is called to Diagram A above, in which are illustrated both the threshold dose (i. e., the minimum dose producing the initial or lowest level of response, tagged on Diagram A as dose level 2) and the minimum dose producing maximum response (tagged as dose level 3 on Diagram A); each of these could be defined as minimum effective doses, according to whether "effective" were interpreted as applying to "lowest or initial response" (i. e., threshold response) or to "maximum response". Indeed, beyond these two possibilities, an author may consider any point of response between the actual minimum and maximum responses as the point of adequacy for the specific use for which the compound is intended and define the dose producing that level of response as being "effective".

When dealing with specific responses that exhibit graduation of degree below the maximum (i. e., responses illustrated in Diagram A), the CBCC uses the term "minimum effective dose" to be synonymous with "threshold dose" and CBCC coding and interpretation should be based on this definition of "minimum effective dose".

If the author uses the expression "minimum effective dose" and it is described by the author or otherwise recognized as being actually anything higher than threshold dose (e. g., if it is the minimum dose producing maximum response when maximum response is greater than threshold response) a criterion other than Criterion 20 must be used.

When dealing with responses of the type illustrated by Diagram B (i. e., death or a response of the "all-or-none" type), the expression "minimum effective dose" is not ambiguous when referring to a test involving only a single individual's response; as the chart indicates, there is only one level that the expression "minimum effective dose" could describe under these circumstances, since there is essentially only one response level. However, tests involving such responses as Diagram B illustrates frequently employ more than a single test individual, with the result that the data are expressed as a minimum dose causing death (or an "all-or-none" type of response) in a given percentage of individuals tested. Here, the expression "minimum effective dose" becomes an ambiguity, for the concept of its definition may be according to one author the minimum dose killing one individual of the group, e. g., or it may be established for another author's data as the minimum dose killing 50% of the individuals, or the minimum dose killing all individuals, etc. On the assumption that when the author is determining a "minimum effective dose" as a "minimum lethal dose" or as a "minimum dose causing an 'all-or-none' response", the test was most reasonably devised to determine the dose that would ideally (effectively) assure death or the "all-or-none" response in 100% of the group of individuals, the CBCC has followed, for its coding, a definition of "minimum lethal dose" ("minimum toxic dose") as the smallest dose that kills (or that causes the "all-or-none" type of response in) 100% of the organisms tested. Therefore, when the expression "minimum effective dose" or "minimum lethal dose" is used by the author with reference to a group or population and with no further explanation about the actual per cent of organisms affected or killed, it should be interpreted as the smallest dose killing 100%. Furthermore, since this dose causing response in 100% of organisms tested is demonstrated to be the smallest dose capable of producing that degree of response, it can be correlated with percent response on the Grid, using Criterion 51, 52, or 53; i. e., the dose can be placed on the abscissa of the Grid (at the 99. 99% level) and the Field Y code symbol will be the evaluation area of the Grid in which the dosage falls.

With reference to toxicity determinations of test compounds to be used therapeutically (refer to Diagram B), note that when the author has determined a maximum dose not causing death (Dose Level 1 of the Diagram), he has had necessarily to determine the minimum dose causing death (Dose Level 2). If the coder has available only the minimum dose causing death, he has no choice but to code it and use Criterion 20 in Field X (or Criterion 51, 52, or 53, under circumstances described in the preceding paragraph). When both levels are given in the author's data, however, the CBCC always prefers to code Dose Level 1 and use Criterion 21 in Field X; while it is true that both of these dose levels reveal the maximum safe level, Dose Level 1 is a more direct statement of this safe level than Dose Level 2.

On the other hand, when compounds are being tested for their ability to kill (i. e., not tested for therapeutically safe levels), the CBCC always codes the dose revealing best the compound's killing potency. This is always Dose Level 2 of Diagram B.

When a biology code line is made to record a chemical's threshold or minimal effective dose, there is no question about the specific response of Field T having been produced nor about the dose being the minimum necessary to cause that particular intensity of response. Therefore, when Criterion 20 is used in Field X, Field W is always coded with Symbol P or Ø (never with Symbol M, since this symbol is used to indicate that the minimum dose needed has not been demonstrated, nor with Symbols L or N which are used only when the minimum response intensity has not been determined, nor with Symbols J, K, or Q which indicate that the response was not produced or was produced only questionably).

15. Criterion 21; maximum tolerated dose; largest dose not producing the response in Field T

In the case of Criterion 21, the fixed level of intensity of response in the individual organism is negative--i. e., non-response: the organism's unresponsiveness which immediately precedes the organism's response as the dose size is increased. With this fixed definition of the response level, the size of the dose becomes the only variable and it is this dose size (coded in Field M, N, or P) on which is based the Field Y rating when Criterion 21 is used.

This criterion is almost restricted in use to the experimental determinations of maximum safe levels of chemicals to be used therapeutically. This is discussed in the two paragraphs before the last, in Division 14. (See the dose level tagged as 1 of Diagram B, Division 14.)

However, Criterion 21 might also be used, as indicated in Diagram A (dose level tagged as 1) of Division 14, when a maximum dose has been determined which does not cause some response other than death (ordinarily some non-lethal toxic response).

When the maximum dose not producing the response (death or otherwise) is determined in individual organisms, Field Y is coded with the dosage rating coded in Column 48 of Field N (or Column 46 of Field M or Column 51 of Field P). The code value of Column 46, 48, or 51 is transferred directly to Field Y as the Field Y rating (rather than inversing it as in the case of Criterion 20). The reason for this is explained as follows.

When Criterion 21 is used, Field T is always coded with the action that is produced (e. g., "death") when a dose is administered that is larger than the dose coded in Field M, N, or P; this Field T coding is desirable in view of the fact that the compound's specific action (e. g., its toxic or lethal quality) had to be demonstrated in order to determine the maximum dose that did not produce the action (e. g., a maximum tolerated dose). At the same time, note that, according to the CBCC coding pattern, when a dose that did not produce the action in Field T is coded in Fields M, N, and P, the failure to produce the response with that dose is always indicated in Field Y by Symbol 1, with Criterion 01, 02, or 62. These coding conventions represent a problem for Criterion 21, since (1) it is desirable to have coded in Field T the action (usually "death") which has actually been demonstrated in the process of determining the maximum dose that did not produce it, yet (2) it is the intention of the criterion to give a rating to the compound according to that largest dose that did not cause the action which means that Fields M, N, and P should be coded with that non-active dose level. The solution lies with the definition of the criterion; contrary to every other criterion of Field X, the definition for Criterion 21 implies that the action coded in Field T was produced but only when a dosage higher than the dose coded in Field M, N, or P is administered. Thus, having Criterion 21 in Field X carries the implication that the response in Field T did not occur at the coded dose level. The criterion then proceeds to rate the test compound, not on its ability to produce the response, but on its ability not to produce the response, a rating as unique in Field Y as the dose is unique in Fields M, N, and P, relative to the action coded in Field T. Consider, to illustrate the Field Y coding, the response, death (Field T), for which has been determined the largest dose not producing it (i. e., the maximum tolerated dose): the smaller the maximum tolerated dose, the greater is the compound's toxic potency; the greater the toxic potency, the less is the compound's ability not to kill (i. e., the less is it safe). Therefore, it can be seen that the smaller the maximum tolerated dose, the smaller is the ability not to kill--a direct rather than an inverse relation. Thus, when Criterion 21 is used, the coding in Field M, N, or P is used directly to rate the compound's ability not to produce the action in Field T.

Field M, N, or P: coding in Col. 46, 48, or 51	Field Y: Coding in Col. 71
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9

The necessity for special interpretation of the code line is demonstrated by the following two examples, designated as A and B:

	Field N	Field T	Field X	Field Y
A.	100 mg (Symbol 27)	Death (Symbol 11)	Criterion 20	3
B.	85 mg (Symbol 27)	Death (Symbol 11)	Criterion 21	7

In interpreting these, if the entry in Field X were ignored, Example A would be read as "the test compound causes death at a dose between 81 and 243 mg (100 mg can not be coded exactly in the dosage fields--only ranges are represented by code symbols of those fields), which means that the compound is not very toxic (a rating of 3 in Field Y)." If the coding of Field X in Example B were ignored, that line would be interpreted in the customary way, i.e., similarly to the interpretation just made for Example A: "the test compound causes death at 81 to 243 mg which means that it is quite toxic (a rating of 7 in Field Y)." However, as has been pointed out, Criterion 21 lends a wholly different interpretation to the line and, therefore, whenever retrieval is made from the CBCC file of coded data and sorting is by the evaluation ratings in Field Y, Field X must be consulted for any IBM cards coded with Symbol 21 and the cards interpreted accordingly. Thus, Example B above, interpreted correctly, reads, "the test compound causes death, but at a dose higher than the dose administered (it may or may not be larger than the highest dose of the range coded in Field N, as explained in the following paragraph, and the compound is rated as being relatively safe as a therapeutic agent (a rating of 7 in Field Y), as indicated by Criterion 21 in Field X."

The examples given here illustrate the fact that the procedure of coding doses (which means coding, by a given symbol, a range of doses) in Fields M and N, rather than literally recording and punching the dose itself has the disadvantage that the Biology Code Sheet must always be consulted for the actual value, which is coded only as being somewhere within a specified range of values. In the examples above, 85 mg did not cause the response while 100 mg did cause it; the coding for this in Field N could just as well mean that 200 mg did not cause the response while 225 mg did cause it, since the symbol coded in Field N represents a range of 81 through 243 mg; the Biology Code Sheet must be consulted to learn the actual maximum tolerated dose or the threshold dose of this particular compound, since the coder always writes the actual dose on the Code Sheet in addition to coding it. The procedure of coding doses as is done in Fields M and N is based on the attitude that the literal recording and IBM punching of an exact dose value, even in the case of maximum tolerated dose or threshold dose, is less important than being able to sort out from the coded files data on all test compounds causing responses at dosages below, above, or between certain levels, which purpose is accomplished with adequate efficiency and with the minimum use of space on the IBM punched card (a single column in each of Fields M, N, and P) by coding the dose range.

A maximum tolerated dose level, like a minimum effective dose level (threshold level), may be determined for each individual of a group of individuals, demonstrating the variation between individuals for tolerating the test compound. (See Division 14, paragraph 8.) In this case, Criterion 51, 52, or 53 is used in Field X and the rating for Field Y is found by plotting on the Grid the maximum tolerated doses against the corresponding percentages of organisms responding at those dose levels.

If the author merely expresses the maximum tolerated dose as a range (e.g., "20 to 30 mg is the maximum dose tolerated by the individual" or "20 to 30 mg is the maximum dose tolerated by 75% of the individuals tested"), the CBCC codes the dose in Fields M, N, and P as an average of the limits of this range and the Field Y rating is derived directly from the dosage field or through the Grid.

When tests have demonstrated the maximum tolerated dose (or the largest dose not causing a non-toxic response) and code evaluation is by Criterion 21, Field W is coded with Symbol Ø or P. (See the diagrams of Division 14.) This follows the pattern of coding maximum tolerated dose determinations, by which Field T is coded with the response which the dose coded in Fields M and N does not cause. In other words, Field W is coded to indicate that the response coded in Field T has been produced and the lowest dose that will cause the response to any degree has been determined (it does not indicate that the dose coded in Field M or N is not that threshold dose, however); Symbol 21 in Field X provides the coding clue to the fact that the dose in Field M or N is actually a concentration or quantity below the threshold dose and that the evaluation in Field Y is not an evaluation of the compound's killing ability but an expression of its degree of safety.

16. Criterion 22; antagonism; the potency of the test compound for antagonizing COMPLETELY a biological response to a secondary compound

As its definition indicates, Criterion 22 is specifically for rating test compounds by a particular chemical action, inhibition of another chemical's action on a biological system.

It might be argued that the action of one compound on another is not a biological action under any circumstances (even when the compound affected is a compound acting on a biological organism and the action of this affected compound is the aspect affected by the test compound). Nevertheless, a test compound's effect on the biological action of another compound is of such significance that it is justifiable devising a way of recording and coding it.

The special criteria that have been included in Field X for coding an effect of a test compound on the biological action of another compound (hereinafter referred to as the "secondary compound" to distinguish it from the test compound) are Criteria 22 and 55, which are used, under special conditions described in this division, to rate antagonistic effects. Synergism, which is another effect a test compound may have on the biological action of a secondary compound, is evaluated by Criteria 61 and 62, which, however, are not exclusively for evaluation of synergism.

In connection with Criterion 22 (as well as with Criterion 55), it is worth noting here that Field T-1 has been equipped with the term "antagonizes" (Symbol 9 of Field T-1) as an action of the test compound and since the test compound's net effect is the antagonism of the specific biological response to the secondary compound, this biological response to the secondary compound is coded in Field T-2. Unfortunately, it is not possible to code the secondary compound's specific action in Field T-1, inasmuch as Field T-1 has been used for indicating the test compound's inhibitory action; therefore, it is always necessary to consult the written abstract on the Biology Code Sheet to learn the secondary compound's action inhibited by the test compound. (See also Field T-1, Item 3 of Division 12.)

Criterion 22 (as well as Criterion 55) can be regarded as placing a rating on the potency of the test compound for performing the specific activity; in other words, it is rated according to the amount of the test compound necessary to perform a definite level of activity in individual organisms. In the case of both Criteria 22 and 55, the intensity of response in individual organisms is assumed to be the complete antagonism (100%) of whatever response the secondary compound produced in the test organism when administered alone. (I.e., the criteria are not intended for incomplete antagonism, such as "X units of test compound, when administered with Y units of secondary compound, antagonized 50% of the action of the secondary compound administered alone.") This is explained in the second paragraph below. With the intensity of response in individual organisms fixed by definition at 100%, the test compound's potency is then dependent solely on the quantity needed to bring about this complete antagonism of the secondary compound's biological action. This potency is not expressed merely as the dosage coded in Field M, N, or P (as is the case with Criterion 20, or with Criterion 21), but is expressed by comparing the quantity of the test compound needed to antagonize completely the secondary compound's biological action to the quantity of the secondary compound that was antagonized. The resulting value is then coded by reference to a special Field Y scale accompanying Criterion 22, from which a Field Y code rating is derived.

The explanation for the assumption of 100% antagonism for Criterion 22 (and Criterion 55) lies with the procedure for deriving the Field Y evaluation. If it is assumed that the antagonism of the secondary compound's action can be accomplished by test compounds at varying degrees less than 100%, the quantity of test compound needed for a lower degree of antagonism (40% or 75% antagonism, e.g.) should presumably be less than the quantity needed for complete antagonism. If the degree of antagonism is ignored and the quantity administered causes less than complete antagonism, the dosage ratio and Field Y code evaluation will be too low. The CBCC has established no criterion for the specific case of antagonism known to be less than 100%. If the test compound proves incapable of antagonizing completely the secondary compound's action, regardless of the quantity of test compound administered, or if the highest dose of test compound administered causes less than complete antagonism (without demonstrating that this is the maximum intensity of antagonism of which the test compound is capable), only Criterion 62 (percent response) is available for recording the degree of antagonism regardless of the quantity of test compound needed to produce that degree. This is discussed further in the second paragraph of Division 21.

It may not be immediately clear the reason for establishing evaluation on the basis of a correlation of the dose of test compound with the dose of secondary compound; consideration of all the factors involved tends to be confusing. It should be observed that (1) the specific response of the test organism to the secondary compound may characteristically vary in intensity, according to the size of dose of secondary compound administered and (2) the dose of secondary compound administered in the test need not always be assumed to be the minimum dose needed to cause the maximum intensity of response. In many cases of antagonism, the size of the dose of test compound needed to antagonize the secondary compound's biological effect depends upon what total quantity of secondary compound the test compound must act upon, since the antagonism is regarded as purely an interaction between the two compounds. Thus, (1) if the intensity of biological response to the secondary compound can vary or (2) if the dose of secondary compound were higher than needed to produce the organism's response intensity (this response intensity's reduction being the only clue to antagonistic activity of the test compound), it will be seen that the dose of secondary compound might be a variable and consequently the dose of test compound needed to antagonize it would be a variable. In other words, considering possibilities (1) and (2) above, it is possible that the test could be repeated, employing in the second test a dose of secondary compound larger or smaller than the dose administered in the first test, to induce adequately the same biological response. The response in the second test would subsequently be shown to be antagonized by a dose of test compound higher or lower, respectively, than in the first test. Thus, if evaluation were based on dose size of test compound alone, without knowing whether the secondary compound dose was the minimum needed for a given response intensity, the expression would be meaningless as an evaluation of the test compound's ability to antagonize the specific response (Field T) of the test organism (Field E) to the specific secondary compound. The only alternative has been to regard antagonism as a quantitative chemical interaction and assume that, when antagonism has been complete (see the preceding paragraph), a calculation indicating what dosage of secondary compound is antagonized by each unit of test compound will represent a reasonable evaluation of the test compound's ability to antagonize the secondary compound relative to the specific response and test organism involved and relative to other test compounds.

In using the dosage ratio for deriving a code evaluation, an assumption is made which should be recognized, namely that the ratio is assumed to be the same, regardless of the size of the dose of the secondary compound. For example, it assumes that when the biological response to a secondary compound, administered at a dose of 5 grams, is completely antagonized by 0.5 grams of test compound, the greater biological response to 50 grams of that secondary compound will be completely antagonized by 5 grams of test compound. This should probably not be assumed and therefore, the code rating derived by Criterion 22 should always be interpreted in terms of the actual size indicated by the coding in Fields M and N rather than mere relative size of the doses of the test compound and secondary compound, as indicated by the ratio (written on the Code Sheet and by the code symbol in Field Y).

When the antagonism of the response to the secondary compound has been demonstrated to be the maximum antagonism of which the test compound is capable and the test compound dose is the minimum dose producing this degree of antagonism, Field W is always coded with Symbol Ø regardless of whether the maximum antagonism is 100% (Criterion 55) or less than 100% (Criterion 62). As indicated earlier, if the test compound dose is not known to be the minimum dose, Field W should be coded with Symbol M or N. If the antagonism is less than 100% (Criterion 62) and the test compound has not been proved incompetent for causing greater antagonism with larger doses, use Symbol P in Field W. If only one dose is given and less than 100% antagonism results (Criterion 62), code Field W with

Symbol L. If no antagonism appears, use Symbol J or K, according to whether the largest dose administered was the maximum tolerated dose; these negative data, however, must never be coded with Criterion 22, but only with Criterion 62 (or 01 or 02) with Symbol 1 in Field Y.

17. Criterion 30; weight of the thyroid gland

Criterion 30 was established for a special coding project the tests of which evaluated each of many compounds on the basis of its ability to increase the weight of the thyroid gland--in other words, for the compound's "anti-thyroid" effect for which the hypertrophy of the gland was a criterion. The definition of the criterion specifies the measure of weight as milligrams of thyroid gland per 100 grams of body weight. A special scale accompanies Criterion 30, built on values representing possible thyroid gland weights (expressed as mg/100 gm of body weight). The ranges of these values represent spans of 8 mg/100 gm of body weight; each range, then, is assigned a symbol which is used as the code evaluation in Field Y. As this scale indicates, only compounds that cause more than a four-fold increase in weight are considered highly effective. The criterion does not correlate the intensity of response with the quantity of compound needed to cause that intensity in order to derive the evaluation in Field Y; the Field Y evaluation is only an expression of the intensity of response--the degree of hypertrophy. Thus, with Criterion 30, the test compound's potency is not expressed in Field Y and can be understood only by consulting both Field Y and the dosage fields.

When Criterion 30 is used, the data must be positive, otherwise Criterion 01 or 02 must be used with Symbol 1 in Field Y and Symbols J or K in Field W, according to whether the compound was known to have been administered at the maximum tolerated dose. When the data are positive and Criterion 30 is used, if only one dose regimen were administered, Field W is coded with Symbol L or M, according to whether the dose were known to be the maximum tolerated. It would probably be a rare drug, tested for this special effect and by this technique, which would be tested repeatedly but at different dosage regimens to determine the minimum dose causing a given intensity of response or the dose causing the maximum response below a toxic level. Nevertheless, if these determinations are made, Symbol N, Ø, or P should be used according to their definitions.

18. Criterion 31; iodine content of the thyroid gland

Like Criterion 30, Criterion 31 is a special criterion for anti-thyroid studies. In this case, the test compound is evaluated on the basis of its ability to decrease iodine deposit in the thyroid gland. The amount of iodine in the gland, after prolonged treatment with the test compound, is measured in terms of milligrams of iodine per 100 grams of thyroid weight. A special scale accompanies Criterion 31 whose ranges represent 50% decreases, beginning with a "normal" 40 mg of iodine per 100 gm of thyroid gland. The scale is based on the concept that only compounds that reduce the iodine content to less than 1/8 of that "normal" concentration are to be considered highly effective as anti-thyroid materials.

Coding in Fields X, Y, and W follows the pattern described for Criterion 30 in Division 17 to which reference should be made.

19. Criteria 51, 52, and 53; evaluation of potency of the test compound expressed in terms of percentage of organisms affected relative to the quantity of test compound needed to affect that percentage

Criteria 51, 52, and 53 are used exclusively for evaluating results of tests in which a group of individuals has been administered a given quantity of the test compound or in which several groups have each been administered different quantities of the test compound. The purpose of such tests (sometimes referred to as "population studies") is to determine the percentage of a group of individuals responding to each specific quantity of test compound. In other words, these data are concerned with the variation between individuals of the test organism species and the objective of the test is to determine the minimum quantity of test compound producing a specified response in a given percentage of individuals (e.g., lethal or threshold dose for 50%, 80%, or 100% of the individuals treated) or the reverse, the percentage of individuals giving a specified response to a given quantity of test compound. Under a section of Division 8 designated as Subdivision B, this is described as an expression of potency in terms of dosage vs. percentage of individuals affected at a given intensity of response. The definitions of Criteria 51, 52, and 53 do not bear stipulation of any specific intensity

of response in the individual organism; for example, the definitions do not specify that the response is the threshold response, or 50% response, or 80% response, etc., in the individual.

However, Criteria 51, 52, and 53 have been generally intended for evaluating responses of the "all-or-none" type (which responses display no graduation of intensity--in particular, death) or threshold intensities of other responses. (See Division 14.) As with Criterion 20, when the response is "death" or other all-or-none response of the individual, the "potency" of the test compound for producing the response in the individual can be expressed solely by the quantity needed to produce that intensity in the individual. This quantitative dosage value, therefore, can be correlated with the third factor, the percentage of individuals responding; the percentage-of-individuals value might also be regarded as an "intensity" of response, in terms of population response. When the response is not death or other all-or-none response of the individual, Criterion 51, 52, or 53 can be used only by ignoring the factor of variation of response intensity in the individual (or by redefining the criteria, setting this variable at a fixed intensity level, such as 100% response in each individual).

The quantity of test compound administered is expressed in Fields M, N, O, and P. Of these, Fields M, N, and P (concentration, quantity per unit of administration, and duration of administration, respectively) are most significant in expressing actual measure of total quantity. Variation in quantity of the test compound can be in terms of variation in any of these fields. Thus, three criteria are provided to distinguish the terms in which the dosage is expressed: Criterion 51 (concentration vs. percentage of organisms responding), Criterion 52 (quantity per administration or per unit time vs. percentage of organisms responding), and Criterion 53 (duration of administration of a standard concentration or quantity vs. percentage of organisms responding). It is not inconceivable that the variant in an experimental dosage regimen might be the frequency of administration (Field O) rather than dose concentration, quantity, or duration of administration. However, no special Criterion has been established for correlating frequency of administration with percentage of individuals responding.

To derive a code evaluation with Criterion 51, 52, or 53, the two factors involved are correlated on the special Log-Probit Grid, described in Division 24. This Grid is used by the CBCC for all fields of biology testing (insecticide, herbicide, enzyme, pharmacology, etc.) when (and only when) the data are expressed in terms of the two variable factors, (1) percentage of organisms responding to the test compound vs. (2) either the dose causing that response (as in the case of Criterion 51, 52, or 53) or a time factor (as in the case of Criterion 54). When administration has been made at only one dosage level and the percentage of individuals responding has been determined, this single correlation can be made on the Grid and the evaluation area (1, 3, 5, 7, or 9) in which the correlation point falls will provide the symbol for coding Field Y. If a series of tests are run, each with different dosage levels, and the percentages of organisms responding to each level are determined, each dosage can be correlated with the percentage of individuals responding to that dosage; a line drawn to connect these several points on the Grid will indicate, by its relation to the areas of the Grid, the evaluation symbol to be used in Field Y, as described in Division 24.

20. Criteria 54, 57, 58, and 59; evaluation of intensity of response expressed in terms of the percentage of individuals affected relative to the time value (Field U) connected with the response

Reference should be made to Division 10 which describes Criteria 10, 11, 12, and 13 relative to their expressing evaluations in terms of potency of the test compound for producing the response.

Test compounds are frequently evaluated in terms of the relative speed by which they produce a specific response, or by relative duration of the response they produce, etc. When evaluation is based on only this time value, one of Criteria 10, 11, 12, or 13 is used. Further, when Criterion 10, 11, 12, or 13 is used, it is assumed that the determination was made on a single individual or that it represents a general evaluation of response for all individuals of the test organism species. However, occasionally, tests demonstrate the incidence of a given time value in a group of individuals administered a given dose (e.g., the percentage of individuals which were killed within 10 minutes or the percentage killed within 24 hours at the dose size administered). The test compound that kills fewer organisms in a longer time is less valuable (as a killing agent) than a test compound that kills more individuals in a shorter time, using a standard dose.

To correlate this time value with the percentage of individuals responding, the CBCC uses the same Log-Probit Grid as is used for Criteria 51, 52, and 53 (the latter criteria correlating dose size with percentage of individuals responding). This correlation of time values with percentage of

individuals responding is not an expression of potency which is defined in Division 8 as a correlation of dose size and intensity of response.

The CBCC has devised no coding criterion for correlating intensity of the action in terms of time values (duration of action, time to specific action, etc.) with the intensity of response in terms of percentage of response in the individual organism (e.g., "Compound A caused 10% increase in blood pressure for 30 minutes", or "Compound B caused 10% increase in blood pressure for 2 hours", or "Compound C caused 50% increase in blood pressure for 30 minutes").

Criteria 54, 57, 58, and 59 can be used when the data consist of the incidence (in a group of organisms) of a given time value (a duration of action, a time of specific action, etc.) at one given dose level--or of the incidence of each of several time values (several durations of action, e.g.) at one given dose level. For example: "In 25% of the individuals administered 50 mg/kg, the response lasted 5-10 minutes; in 40% of the individuals (administered that same quantity of test compound), the response lasted 10-20 minutes; in 20%, the response lasted 20-25 minutes; and in 15%, it lasted more than 25 minutes". To derive a code evaluation from these data, the Grid is used, plotting on it the several coordinates (the several durations of response with the cumulative percentages of organisms responding for each duration). The following outline for the example above will be helpful as a general illustration of the use of the Grid for evaluation by those four criteria. In this particular example, Criterion 54 would be used. Note also that when using Criterion 54, the reciprocal of the symbol coded in Column 66 of Field U is used as the value plotted on the abscissa of the Grid. This is explained in Division 8 of the Specific Directions and Explanations of Field U.

Duration of Response	Symbol for duration of response in Column 66 (Field U)	Symbol for use on the ordinate of the Grid	Cumulative percentage of individuals showing duration of response. The response endured for:
5-10 min.	4 (Scale 4)	6	at least 5-10 minutes in 100% of individuals
10-20 min.	5 (Scale 4)	5	at least 10-20 minutes in 75% of individuals
20-25 min.	6 (Scale 4)	4	at least 20-25 minutes in 35% of individuals
>25 min.	6 (Scale 4)	4	more than 25 minutes in 15% of individuals

On the Grid, the position and slope of the distribution curve, shown by a line connecting the four coordinates of this example, indicates the evaluation to be coded in Field Y, according to the area of the Grid in which it falls. Evaluations of all compounds tested for a given action and evaluated by Criterion 54 tend to be comparable by virtue of the fact that those evaluations were made with reference to the same fixed areas of the Grid. If the curve occurs on the right hand side of the Grid, a low intensity of response is indicated (note again that this is not an expression of "potency", since the dose size is not correlated here); the further the curve occurs toward the left edge of the Grid, the higher the intensity of response is indicated to be. However, relative to this evaluation, reference should be made to the fifth and sixth paragraphs of Division 10, pointing out that evaluations of Criterion 10, 11, 12, and 13 are largely dependent on the coder's judgment in selecting an appropriate scale in Field U; this factor plays the identical role with Criteria 54, 57, 58, and 59. The positions of the curve on the Grid (right or left) is dependent on the coder's choice of scale in Field U.

The following sample data illustrate for each of the four criteria the way the cumulative percentage of organisms responding is plotted on the Grid to derive an evaluation of the intensity of response to the dose administered and coded in Fields M, N, O, and P.

Criterion 54: 30 minutes after the response began, it had ceased in 80% of the individuals to which the test compound had been administered at the coded dose; 50 minutes after the response began, it had ceased in 100% of the individuals. Here, 80% and 100% (99.99%) represent the points to be plotted on the ordinate of the Grid. The reciprocal of the value coded in Column 66 of Field U is to be plotted on the abscissa.

Criterion 57: 20% of the individuals to which the test compound had been administered at the coded dose survived 2-3 hours longer than controls, 60% survived 3-4 hours longer than controls, 15% survived 4-8 hours longer than controls, and 5% survived 8-10 hours longer than controls. Interpretation of these data for plotting on the Grid (the following percentage figures represent the points to be plotted on the ordinate of the Grid): 5% of the individuals survived 8-10 hours longer than controls, 20% of the individuals survived 4-8 hours (or more) longer than controls, 80% survived 3-4 hours (or more) longer than controls, and 100% survived 2-3 hours (or more) longer than controls. The reciprocal of the value coded in Column 66 of Field U is to be plotted on the abscissa.

Criterion 58: 20% of the individuals to which the test compound had been administered at the coded dose responded in 5-6 minutes, 40% responded in 7-8 minutes, 30% responded in 9-10 minutes, and 10% responded only after 15 minutes. Interpretation of these data for plotting on the Grid (the following percentage figures represent the points to be plotted on the ordinate of the Grid): 20% of the individuals responded in 5-6 minutes, 60% had responded after 7-8 minutes, 90% had responded after 9-10 minutes, and 100% had responded only after 15 minutes. The value coded in Column 66 of Field U is to be plotted on the abscissa.

Criterion 59: 10% of the individuals to which the test compound had been administered at the coded dose were dead after 1 hour, 40% were dead after 90 minutes, 80% were dead after 2 hours, 90% were dead after 3 hours, and 100% were dead after 8 hours. Here, 10%, 40%, 80%, 90%, and 100% represent the points to be plotted on the ordinate of the Grid. The value coded in Column 66 of Field U is to be plotted on the abscissa.

Criterion 54, 57, 58, or 59 can only be used if the test compound actually produces the response coded in Field T. (If the response were not produced, only Criterion 01, 02, or 62 would be used with Symbol 1 in Field Y.) Therefore, Symbol J or K would never be used in Field W when Symbol 54, 57, 58, or 59 is coded in Field X. If the test compound has been administered only at the maximum tolerated dose, Field W is coded with Symbol M. If the dose administered in the test being coded is known to cause the greatest duration of response (or the greatest increase in survival time, the shortest time to specific action other than death, or the shortest killing time) of which the test compound is capable, Field W is coded with Symbol Ø or N, according to whether the dose was known to be the minimum necessary to cause that maximum intensity of response. If the dose administered in the test being coded is not demonstrated to cause the maximum intensity of which the compound is capable (i.e., the greatest duration of response, shortest killing time, etc.), but is known not to be in excess of the amount needed to cause the maximum intensity of response, code Field W with Symbol P.

21. Criterion 55; evaluation of potency of the test compound in terms of the antagonism ratio (relative quantities of antagonized compound and antagonist) correlated with the percentage of organisms responding

Reference should be made to Division 16 which describes Criterion 22 and explains that that criterion as well as Criterion 55 can be used only when the response produced by the secondary compound administered alone is antagonized 100% by the test compound. In the case of Criterion 22, a code rating is derived by simply relating dosage sizes of the secondary compound and the test compound (deriving an antagonism ratio). In the same way, a dosage ratio is calculated for Criterion 55; the quantity of test compound needed to antagonize completely the action of the secondary compound is related to the quantity of secondary compound antagonized. The ratio, as established for Criterion 22, is reversed in Criterion 55. As in the case of Criterion 22, the ratio can be placed on a special scale accompanying Criterion 55 in the Code. By this scale, dose values are derived (1-9) which, unlike Criterion 22, are not used directly as code symbols but are correlated with the percentage of individuals in which antagonism was accomplished by the dosage indicated by the antagonism ratio. The correlation is made by the Log-Probit Grid. The dosage ratio is reversed from that used for Criterion 22 because of the use to be made of the ratio on the Grid. The ratio of Criterion 22 will be seen to express the amount of secondary compound antagonized by each unit of test compound. Criterion 55, however, is concerned with comparing all test compounds on the basis of the amount of each test compound capable of antagonizing a unit of the secondary compound, this amount of test compound being related to the percentage incidence by the Grid.

As the discussion of Division 16 has indicated, the CBCC has devised no code criterion for data in which antagonism is demonstrated to be of some degree of intensity less than 100% in the individual organism (e.g., "50% inhibition of the muscle contraction caused by the secondary compound"). At present, this incomplete inhibition can be coded only by evaluating merely on the basis of percentage inhibition (Criterion 62), ignoring the dosage ratio. As has been suggested, in the final paragraphs of Subdivision A in Division 8, a dosage-response intensity correlation might be possible by devising a special grid on which the highest percentage antagonism (in the individual organism) of which the compound is capable is correlated with the minimum dose (an antagonism dose ratio) demonstrated to be capable of causing that degree of antagonism. This would supplement Criterion 22 by providing an expression of relative potency (for antagonism in the individual organism) for each test compound, which Criterion 62 can not provide.

If data occur in which dosage size and percentage of individuals responding are correlated (as with Criterion 55) but, in addition, the antagonism of the response to the secondary compound is less than 100% in the individual organism, it is suggested that a new criterion be established, bearing in its definition the stipulation that the dosage size and percentage of individuals responding are correlated and that the degree of antagonism in the individual is less than 100% (either ignoring this degree of antagonism in the individual or establishing a special criterion for each standard level such as 50% antagonism, 80% antagonism, etc.)

When Criterion 55 is used, antagonism of the secondary compound's action has been demonstrated by the test, otherwise it would be negative data coded by Criterion 01, 02, or 62 with Symbol I in Field Y and Symbol J or K in Field W. Therefore, when Criterion 55 is used, Field W is coded with Symbol L or M, if only one dose were tested and complete antagonism occurred in less than 100% of the individuals tested. If several tests were run, each at different dosage levels, so that a curve is drawn on the Grid, Field W is coded with Symbol Ø or P, according to whether one of the doses tested produced complete antagonism in 100% of the individuals tested and is the minimum dose needed to cause complete antagonism in 100% of the individuals (Symbol Ø) or whether the highest dose administered did not produce the antagonism in 100% of the individuals tested (Symbol P). If all doses tested cause complete antagonism in all individuals tested (100%) to which those doses are administered, Criterion 55 cannot be used, but only Criterion 62 with Symbol 9 in Field Y and with Symbol N in Field W.

22. Evaluation of synergism in Fields X and Y

Synergism, like antagonism, is an effect of one compound (the test compound) on the biological response to another compound (the secondary compound) and it is defined and discussed in the section on Specific Directions and Explanations for Field T-1 (Division 12). Its occurrence is indicated by code in Field T-1 with Symbol 8.

One distinction between synergism and antagonism is that antagonism has a well-defined limitation of maximum intensity (i.e., 100% response intensity) beyond which the test compound action can no longer be defined as antagonism, but only as a reversal of the response to the secondary compound. Synergism, on the other hand, is limited only by the individual characteristics of the organism, of the secondary compound, and of the test compound; it can be less than 100% increase of the response to the secondary compound when administered alone, but it can also be more than 100% increase.

Thus, in the case of synergism, there is no point analogous to the point in antagonism described as "complete" antagonism, except by the limitations on a specific synergistic action imposed by the factors just mentioned as characterizing the specific testing situation. Consequently, in the case of synergism, both of two variables need always to be coded to permit subsequently an evaluation of the test compound's relative potency as a synergist: (1) the degree of synergistic action and (2) the minimum quantity of test compound necessary for that degree of synergism. Note that, when coding antagonism (Criterion 22 or 55), the degree of antagonism is not coded.

As with Criteria 22 and 55, no standard mechanism has as yet been devised by the CBCC for correlating these two factors to derive a single comparative evaluation figure, though a special grid suggested in the discussion of Criterion 22 (see the second paragraph of Division 21) might be adaptable to synergism data.

Lacking a means of correlating the two factors, dose size and degree of synergism, the most reasonable basis for evaluation has seemed to be the maximum degree of synergism of which the test compound is capable. (Although it is probably not always true that the testing procedure guarantees to have demonstrated this maximum capability of the test compound, it is apt to be most often the maximum.) Thus, the Field Y evaluation of synergism is not based on dose size nor is it a correlate of dose size and degree of synergism (in contrast to the evaluation of antagonism which is based on dose size).

The CBCC has rather arbitrarily designated two synergism intensity categories, one consisting of test compounds which can synergize the secondary compound action only to 100% or less than 100% and a second consisting of compounds that synergize actions to a greater degree than 100%. These are coded by two separate criteria in the Code, Criterion 62 for 100% and less than 100% response and Criterion 61 for more than 100% response. The second factor, dosage size of the test compound, is also important, and in interpreting the comparative ability of a test compound for synergizing a specific secondary compound's action, reference must be made to the relative quantities of test compound (synergist) and secondary compound (compound whose action is synergized), as compared to the ability of other test compounds for synergizing the same secondary compound's action. In other words, the interpreter of the code line must relate the evaluation of Field Y to the dose coded in Field M or N (test compound) and to the quantity of secondary compound which should be written in Field D by the coder.

It should be mentioned that prior to this edition of the Code, synergism was given a code evaluation according to special criteria (designated as Criteria 56 and 60). Criterion 56 involved a dosage ratio similar to that of Criterion 55 (the quantity of synergist divided by the quantity of compound synergized) which provided a relative dosage value which in turn was correlated on the Grid with the intensity of synergism (percentage increase in the response to the secondary compound). Criterion 60 was used for evaluation of synergistic response intensities of more than 100% and based evaluation merely on the intensity, attempting no correlation with dose size. In the present edition, Criterion 60 has been omitted, since it provided nothing more than does Criterion 61 (if Field T-1 is coded properly with Symbol 8). Criterion 56 has been omitted because its use of the Grid for correlating relative dose size and degree of synergism has not seemed to be an accurate procedure and because it would seem that if synergism of greater intensity than 100% is to be evaluated according to its intensity only, it may as well be coded consistently by that procedure, even when less than 100%.

If the synergistic activity has been demonstrated to be the maximum intensity of which the test compound is capable, Field W should properly be coded with Symbol N or Ø, according to whether the dose coded in Field M or N is known to be the minimum needed. If the dose is known to be either less than the minimum needed to cause maximum intensity of response or the minimum needed to cause maximum response, but it is not known which, code Field W with Symbol P. If the test compound is administered at only one dose level which is therefore not known to be the dose causing maximum synergism of which the compound is capable, nor the minimum dose needed to cause the synergism produced, Field W would be coded with Symbol L or M, according to whether the dose administered is known to be the maximum tolerated. If the test compound proved incapable of causing synergism, Criterion 62 must be used (or Criterion 01) with Symbol 1 in Field Y and with Field W coded with Symbol J or K, according to whether the dose was administered at the maximum tolerated level. This is discussed in the last part of the section on General Use.

23. Criteria 61 and 62; evaluation based solely on intensity of response regardless of the quantity of test compound

These criteria are used for specific responses (including synergism and antagonism) which may occur at various degrees of intensity in the individual organism. (See Subdivision A of Division 8.) Criteria 61 and 62 make no correlation between the intensity of response (percentage response in the individual organism) and the minimum quantity needed for that response (coded in the dosage fields) to derive a Field Y evaluation expression. Therefore, the evaluation afforded by Criterion 61 or 62 is not an expression of the test compound's potency as it is defined in Division 8. Criteria 61 and 62 represent two categories of response intensity, 62 being for no response and for responses of 100% or less and 61 being for responses of more than 100%.

Criterion 61 or 62 must be used whenever the biological response is of the type that occurs at various intensities beyond the threshold response intensity in the individual organism and the author

expresses the evaluation in terms of the percentage of response in the individual. Field X has no criterion which correlates this intensity of response in the individual with the minimum dose needed for that intensity, with the possible exception of Criteria 20 and 21 which can be considered to base evaluation on dose size alone yet express potency when the response intensity can be ignored. (See Divisions 14 and 15.) Criterion 61 and 62 are used to evaluate synergism as described in Division 22.

Criterion 62 is used for all negative data expressed at 0% response. (All other negative response expressions, either verbal ["inactive", "no response", etc.] or author's scoring symbol ["0", "-", etc.] are coded by Criteria 01 and 02.)

The CBCC has also used Criterion 62 for another evaluation expression--the percentage of individuals (of a group) responding to the test compound (at a given level of intensity of response in the individual). This is distinct from the expression "percentage of response intensity of which an individual is capable" and therefore it is suggested here that, for the expression "percentage of organisms responding at a given response intensity", a unique code symbol (i.e., a distinct criterion) should have been established (e.g., a criterion designated as 63). This use which has been made of Criterion 62 is described in the following paragraph.

It will be noted that whenever a group of organisms is administered the test compound at a given dosage level (a "population study") and the incidence of response is recorded as the result of the test (i.e., the percentage of individuals responding at that dose level and that intensity of individual response), the Log-Probit Grid is used to correlate the percentage of organisms responding with the minimum dose affecting that percentage of organisms to the given degree ("potency" as defined in Subdivision B of Division 8). For this, Criteria 51, 52, and 53 are most frequently used, though Criterion 55 is also established to correlate the percentage of organisms in which a given dose of test compound antagonizes a secondary compound to a given intensity in the individual (100%); also, Criteria 54, 57, 58, and 59 use this Log-Probit Grid, not to derive an expression of potency, but to correlate duration of a specific action, time to a specific action, etc., with the incidence of the duration of action, time to specific action, etc., in a group of individuals all of which are administered the same dose. (See Division 20.) However, evaluations have been made by the CBCC based solely on the incidence of a given response intensity in a group of individuals, disregarding the quantity of test compound, coded in Fields M and N, needed to accomplish that incidence, using Criterion 62, as indicated above. In order for such evaluations to be meaningful (in terms of being subsequently able to compare test compounds for a specific action), it should be assumed that the test of each compound has demonstrated the maximum percentage of organisms the compound is capable of affecting to the given intensity. (Field W should therefore be coded with Symbols N, Ø, or P according to whether the dose has been demonstrated to be the minimum needed). If the percentage of organisms affected has not been demonstrated to be the maximum number the test compound can affect (Field W coded with only Symbol L or P), evaluation of the test compound's potency by correlating coding of Field Y with that of Fields M and N is more uncertain.

24. The Log-Probit Grid; Use of the Grid with Criteria 51, 52, 53, 54, 55, 57, 58, and 59

Each of the criteria which base evaluation on the incidence of the specific response in a group (or "population") of individuals is discussed separately; see Division 19 (Criteria 51, 52, and 53), Division 20 (Criteria 54, 57, 58, and 59), and Division 21 (Criterion 55), as well as Division 22 (Criterion 62), since Criterion 62 is used to evaluate on the basis of the percentage of individuals responding. Reference should also be made to Division 8, particularly the Subdivision B.

Of these criteria, eight (i.e., all except Criterion 62) are concerned with a second factor, either (a) the minimum dose needed to cause the demonstrated incidence of response or (b) the time factor involved in the measurement of the test compound's action (e.g., time to specific action, duration of response, etc., coded in Field U) as related to the incidence of that time factor in a group of individuals. The first of these, (a), represents the second factor for Criteria 51, 52, 53, and 55, while the last, (b), represents the second factor for Criteria 54, 57, 58, and 59.

To correlate the two factors involved in each of these criteria in a way that will provide a basis for comparative code evaluation, the CBCC has established a single evaluation reference chart, using a special graph paper, most frequently referred to as probability paper. The unique feature of this paper is its vertical scale (the ordinate) which is neither arithmetic nor logarithmic; the paper

has been specially scaled so that a cumulative normal distribution curve assumes the form of a straight line. (The horizontal scale of this paper is arithmetic.) The paper is frequently used to indicate how nearly a given set of test results (involving distribution of response within a group of individuals) approaches or deviates from the "normal" distribution curve by observing how the data plotted on the paper deviate from a straight line.

A modification of this probability graph paper consists of applying a logarithmic horizontal scale rather than an arithmetic one. This paper is referred to as logarithmic probability paper and it is employed for asymmetrical distribution curves when this asymmetry is due to the peak of the distribution curve occurring to the left (the curve being described as "skewed to the right"), illustrated in Figure A below.

For biological data in general, the CBCC has used a logarithmic scale on ordinary probability paper. (The horizontal scale of this paper is ruled as an arithmetic scale, but on this arithmetic scale are placed the consecutive ranges of dosage scales of Field M or N or of the time scales of Field P or U, which it will be noted are logarithmic. Observe the code scales of Fields M, N, P, and U.) The following example (a table of simple data and two figures) illustrates the dosage/percentage-organisms-responding data and the distribution curves depicting these data (response distribution curve, Figure A, and cumulative response distribution curve, Figure B).

Dose causing the response (or dose causing death)	Percentage of individuals showing a specific response intensity (or percentage of individuals killed)	Cumulative percentage of individuals
2.5 mg	10% show response	a total of 10% respond
5.0 mg	an additional 32% show response	a total of 42% respond
8.0 mg	an additional 28% show response	a total of 70% respond
12.0 mg	an additional 20% show response	a total of 90% respond
15.0 mg	the final 10% show response	a total of 100% respond

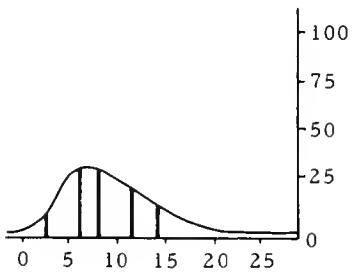


Figure A

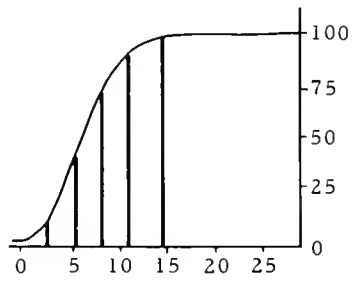


Figure B

It is the cumulative distribution curve, Figure B, or any points thereon, that can be placed on the logarithmic probability chart used by the CBCC, referred to hereafter in this division (and elsewhere in the Code and Key) as the Log-Probit Grid or merely as the Grid.

For any given test compound, it should be understood that all points on any one cumulative distribution curve (Figure B) must be represented by a single code evaluation in Field Y. This is also true of this curve when it is plotted on the Grid and when it therefore is transformed to more nearly approach a straight line. In other words, any data placed on the Grid represent a cumulative distribution curve (transformed to a straight line) or (if none of the doses administered cause the given response intensity in 100% of the organisms tested), it represents a part of the total cumulative distribution curve and it is this curve's position on the Grid (or the position, on the Grid, of that demonstrated fragment of the curve) that must be the basis for an evaluation of the compound's potency for affecting all individuals of the test organism species or strain.

If a test compound characteristically produces the response in a large percentage of individuals when administered in small quantities, its curve will fall on the upper left area of the Grid, whereas if the test compound characteristically produces the response in a small percentage of individuals when administered in large quantities, its curve will fall on the lower right area of the Grid. Therefore, those compounds whose curves occur furthest to the lower right corner of the Grid are rated as the compounds lowest in effectiveness (i. e., the compounds having lowest potency) and those whose curves occur furthest to the upper left corner are rated as highest in effectiveness (highest potency).

The total two-dimensional range from the left to right sides of the Grid (i. e., the total area of the Grid) has been divided into smaller ranges. A range on the lower right has been fixed as representing low activity and a similar range on the upper left has been fixed as representing high activity. Between these, the range fixed to represent intermediate activity has been further divided into three intermediate ranges. To each of these ranges has been assigned a code symbol--i. e., a code rating, 9 representing the higher activities, 1 representing the lower activities, and 3, 5, and 7 representing intermediate activities. (Symbol 1 used with criteria employing the Grid is never used to code "no activity" or "no response", as explained in Division 1.)

The lines dividing the Grid into five ranges are representative cumulative distribution curves whose slopes, as well as their positions, are fixed as references for comparison. They accomplish the purpose of establishing a standard or fixed reference by which one compound can be compared to any other compound on the basis of their relative potencies for causing the same biological response in the same test organism species. Although the division into ranges has been arbitrary to some degree, the position and slope of the fixed reference lines dividing the Grid into the five areas were determined as being reasonable from a study of a variety of actual test data.

Beyond the general position on the Grid, it is not to be supposed that all distribution curves for a given response are alike for all compounds. For example, a given test compound might produce the specific response in a relatively high percentage of organisms at only a small dosage, yet by increasing the dosage to many times the original quantity, the percentage of organisms responding increases very little. This would be in contrast to another test compound which produces the specific response in relatively few organisms at small dosages and when the dose is only moderately increased, the percentage of organisms responding increases to a high level. The first compound's test results would make a low, flat dose/percentage-organisms-responding curve; the second would make a steep curve. Indeed, for any given response, no distribution curve for one compound should be considered to be actually identical to the curve for any other compound. Therefore, not only will the position of the curves plotted on the Grid vary from the exact position of the fixed reference lines (fixed curves) of the Grid, but the slope of the plotted curves will almost invariably deviate from the slope of the fixed lines.

A code designation is made to modify any Grid-derived evaluation coded in Field Y when the slope of the dosage/percentage-organisms-responding curve can be plotted and when, therefore, its deviation one way or the other from the slope of the fixed reference lines (fixed curves) of the Grid is known. This is explained in the following paragraph which, however, discusses first the situation in which only one point or a fragment of the total cumulative distribution curve can be plotted.

Frequently only a single dosage and the single response level produced by that dose are known. In this case, the slope of the dosage/percentage-organisms-responding curve is unknown. It is known that at that given dose, the specific response occurred in that given percentage of organisms and, plotting these two factors on the Grid, the range in which it falls represents the code rating for that compound at that dose level. This rating is comparable to ratings for all other compounds tested for that specific action. It is only when a series of tests have been made using different doses in each test that the dosage-response curve (transformed by the Grid to approach a straight line) can be plotted and it can be seen how it varies from the fixed reference lines of the Grid. If the curve is more shallow (i. e., flatter or more nearly horizontal) than the fixed lines of the Grid, this fact is coded by Symbol # (i. e., the IBM 11 zone punch) in Field Y (Column 71), with the code rating. If the curve is steeper (i. e., more nearly vertical) than the fixed lines of the Grid, this fact is coded by Symbol * (i. e., the IBM 12 zone punch) in Field Y. Only one of the points on this curve which deviates from the slope of the Grid's fixed lines is used to determine a code evaluation rating, the 50% -organisms-responding point. The code designation of the deviation of slope from the slope of the fixed lines indicates whether responses in more than 50% of the individuals (the upper half of the total cumulative distribution

curve) are caused by larger doses (a shallower curve, Symbol #) or by smaller doses (a steeper curve, Symbol *), than would be indicated if the curve were exactly parallel to the fixed lines of the Grid, or whether responses in less than 50% of the individuals are caused by smaller doses (a shallower curve, Symbol #) or by larger doses (a steeper curve, Symbol *).

As indicated above, when any curve plotted on the Grid deviates from the slope of the fixed reference lines of the Grid, the CBCC uses always the evaluation indicated by the point at which the curve of the data crosses the mid-line (the 50%-of-individuals-responding level) of the Grid. If the testing has not been pursued to that point, the curve fragment which can be plotted on the Grid from the data given can ordinarily be extended by interpolation to the mid-line (the 50% level) to determine the appropriate Grid area from which the evaluation symbol should be taken. For example, if the compound has not been administered in sufficient quantity to cause 50% of the individuals to respond or if time values (durations of response, e.g.) have been expressed only in terms of the values for more than 50% of the individuals tested (e.g., durations of response in 100%, 75%, and 60% of individuals, but not the percentage of individuals in which the response may have endured longer), the curve plotted on the Grid would not reach the 50% level, in which case interpolation is indicated as the appropriate procedure for determining an evaluation. When the curve deviates to the extent of falling into two or more areas of the Grid, Field Y evaluation is derived from the area in which the curve, or interpolated curve, crosses the 50% line.

Whenever the above situation exists in which the plotted curve extends into two or more Grid areas (and the area in which the curve crosses the mid-line is used as the evaluation indicator), the CBCC always codes the field from which have been derived the abscissa values (quantitative dosage or duration of administration values, Fields M, N, or P, or special time values, Field U) to correspond to the evaluation expressed in Field Y. In other words, after plotting the curve and after coding Field Y with the value indicated by the area of the Grid in which the curve crosses the mid-line, the coder should study the fragment of the curve that lies wholly within that area of the Grid indicated thereby in Field Y. The extremities of that fragment should determine the coding in Fields M, N, or P (Criteria 51, 52, or 53) or Field U (Criteria 54, 57, 58, or 59). At the upper and lower points where the curve leaves that Grid area, the abscissa should be read (i.e., the bottom, horizontal scale of the Grid--the dosage/time value scale) and these two readings should determine the coding in Field M, N, P, or U, whichever is applicable in the case. If that entire range of doses (or time values) is included in a single code range of the field in question (M, N, P, or U), that field can be coded with a single code symbol; however, if that entire range of doses (or time values) falls in two or more code ranges of Field M, N, P, or U, that field must be double coded to indicate the range over which the Grid evaluation (Field Y) is applicable. The two symbols, * and #, in Field Y indicate that doses (or time values) greater than (or less than) those coded would cause smaller (or greater) percentage response than the evaluation coded in Field Y would indicate.

The following are special observations and directions concerning the use of the Grid, organized as a list of numbered items merely for convenience in reference.

1. For a given dose of test compound (or for a given duration of response, e.g.), the percentage of individuals responding may be reported as a range of response. In this case, code the average of the extremes of the range. For example: "A 5×10^{-2} M concentration of the test compound decreased infestation 30-80%". Here, the CBCC would plot the dose vs. 55% (the average of the range of the percentage of individuals responding), for a single point on the Grid.

2. When a single point is plotted on the Grid (e.g., a single dose administered vs. the percent of individuals responding to that dose) and when it falls exactly on one of the fixed reference lines of the Grid, there is a question of selecting the Grid area to the right or the area to the left of that line for the Field Y evaluation. The CBCC has established the rule of always coding the lower value (i.e., the Grid area to the right of the plotted point), for consistency.

3. When the test has demonstrated only that 100% of the individuals tested respond to the lowest dose administered, there is no assurance that a lower dose, if tested, would not have caused the same intensity of response in 100% of the individuals. The superiority of having determined the minimum dose causing a maximum response of which the test compound is capable is discussed in the section on General Use of Fields W, X, and Y, in explaining the uses of Field W. The Grid can not be used for this data, but only Criterion 62 (or 01) with Symbol M or N in Field W.

When data from tests indicate that the minimum dose needed to affect 100% of individuals has been determined, the Grid can be used to determine the Field Y code evaluation. (This dose being minimum to affect 100% of the individuals tested is evidenced by the laboratory's having administered, of a series of dose levels, at least one dose level which affects less than 100% of individuals.)

4. When plotting data on the Grid, particular attention must be given to the selection of the proper point on the abscissa (the horizontal scale of the Grid). On this scale, each major dividing line marks off a linear section of the scale, there being a total of nine such equal sections of the scale. (Each section can be considered as projecting two-dimensionally as a column across the Grid area.) Each of the nine sections represents one range of a scale of Field M, N, P, or U. For example, the section of the abscissa from the left edge of the Grid to the first of the nine heavier lines dividing the total abscissa represents the first range of any scale of Field M, N, P, or U (e.g., 0.081-0.243 mg [Scale 2 of Field N], or <6 hours [Scale 7 of Field P]). The next equal section of the abscissa scale of the Grid represents the second range of any scale of Field M, N, P, or U, and so on.

Within any of these nine sections of the abscissa of the Grid, the coder should attempt to envision the distribution of values (logarithmic in progression) represented by the particular ranges of dose and time values and thereby select the most appropriate point on this section, rather than place the coordinate arbitrarily anywhere within the section. For example, 0.05 mg/kg (Range 2 of Scale 4 of Field N) would be a point just to the right of the first major vertical dividing line of the Grid, 0.18 mg/kg (also Range 2 of Scale 4 of Field N) would be just to the left of the second major dividing line, and 0.08 mg/kg would be nearly mid-way between the first and second of the dividing lines.

5. In the case of certain biological fields and certain specific responses, even the most effective or "potent" compound or compounds discovered to cause the response produce the specific response only when administered in relatively large amounts. For example, if the most potent compound known for a given response produces the response only when administered in quantities of 1.5 grams or 30-40 lbs/acre, this compound will be evaluated by Criterion 51, 52, or 53 as being "low in effectiveness" (Grid area and Field Y Code Symbol 1 or, at most, 3), regardless of the percentage of individuals (of a group of individuals) affected by this quantity. Unknown compounds tested for that same specific action can be expected to fall in the same general category so that the Grid provides no evaluation distinction between those compounds; in other words, all compounds (even the most effective) tested for that particular action would be evaluated as being low in effectiveness. The same difficulty may occur at the other end of the Grid in the case of other biological responses which occur typically with very small quantities of test compound so that nearly all compounds tested for such a response will fall in area 9 (or 7) of the Grid and be evaluated as being "high in effectiveness".

Actually, the evaluations afforded by the criteria using the Log-Probit Grid are not intended to be evaluations of test compounds' abilities to produce each specific response. (This could only be done if each specific response of Field T-2 were accompanied with special dose ranges typical of that response and if this dose range were then used on the Grid rather than the single dose range now fixed to the Grid.) The general aim of the evaluation field has been to express, whenever possible, the potency of the test compound for producing biological responses in general; if a particular response occurs in most individuals only with a large quantity of test compound, the potency of the compound for that particular action should be regarded as being "low" even if it is the compound with highest potency known for that action; if a particular response occurs in most individuals with a very small quantity of test compound, the potency of the compound for that particular action should be regarded as being "high", even if most compounds causing the response cause it typically with small doses.

This is the purpose of the single fixed Log-Probit Grid. If, in retrieving data evaluated by the Grid, it is discovered that all evaluations for a particular response, or for a particular type of response, appear to be low evaluations (Symbols 1 or 3) or high evaluations (9 or 7), the interpretation should be that the data indicate the response (or the use for which the compound is tested) is of a type for which only large quantities of test compound (evaluation Symbols 1 or 3) are practicable or a type for which only small quantities of test compound (evaluation Symbols 7 and 9) are practicable. The interpretation should not be that, of all the compounds which are found to be evaluated with Symbols 1 or 3, none are practicable for the specific activity (Field T-2).

25. Symbols available for Expansion of Fields W, X, and Y

Field W: As the symbols of this field are defined, they would seem to encompass all basic situations and distinctions for which the field is intended. Symbols 1 through 9 have not been used by the CBCC, but only because they had been used previously for coding information no longer coded because of the infrequency of its use; in another or a special coding project, the former use of Field W, using Symbols 1 through 9, might be restored, if it is of particular importance, or those symbols might be applied to an entirely different type of information, or used for some type of expansion of the use now described for the field. In using Symbols 1 through 9, note that either Symbol * (the IBM 12 zone punch) must not be used or Symbols A through I must not be used; the choice will depend on the comparative advantage of one or the other. Symbol R is still available, of the series formed by using the IBM 11 zone punch (letters J through R) and all of Symbols S through Z are available (formed by using the IBM 0 zone punch).

Field X: Two IBM zone punches (Symbols * and #) have not been given unique meanings in Column 69, so they have been available for forming letters A through R in that column. (The 0 zone punch is used in Column 69 for Criteria 01, 02, 03, and 04.) None of the IBM zone punches (Symbols *, #, and 0) have been used in Column 70 and therefore all numbers and letters have been available in that column. The criteria of Field X have been organized by types, there being certain resemblances between the criteria listed that allow them to be related into series, such as those in the 0- series, in the 1- series, in the 2- series, etc. Since there are fewer criteria in some of these groups than in others, there are fewer symbols of Column 70 available in some groups (the 5- series, e.g.) than others (the 3- series, e.g.). Nevertheless, in existing groups, the room for expansion is far greater than any anticipated need, using numbers and letters in Column 70. In Column 69, numbers 4, 7, 8, and 9 and all of letters A through R are available. In Column 70, all letters are still available and, in most of the groups of criteria, most numbers are still available. IBM punched card retrieval is always more simple when only numerical punches are used and, for that reason, the CBCC would prefer using only numerical symbols when this restriction is practical. If this restriction is observed, symbols of the 5- series of criteria are exhausted, except for 56 (which was used earlier by the CBCC to code synergism and which therefore the CBCC would probably not subsequently use without retrieving all data coded by Criterion 56 and recoding with Criterion 62). In summary, if only numbers are used in Field X, there are four symbols available in Column 69 for new criterion series and, for each series other than the 5- series, a variable number of symbols are available in Column 70 for new criteria of that particular type. If letters should be used for symbols, 22 symbols are available in Column 69; 26 or more are available in Column 70 for each of the symbols used in Column 69.

Field Y: The CBCC has used a maximum of nine symbols in grading evaluation (in some cases, fewer than nine), corresponding to the nine basic punching positions on the IBM card. Thus, it has been possible to restrict coding in Field Y to numerical symbols, avoiding the more complicated retrieval when the IBM zone punch is used for making letter symbols (with the exception of Criteria 62 and 02 which have used the letter A and the 0 zone punch). This means that letters B through R are available for other uses or for additional evaluation gradations.

26. Files of coded biology data arranged by coding in Field W, X, or Y

The CBCC has not established a special file of biology data arranged according to entries in any of Fields W, X, or Y. Retrieval is seldom demanded from these fields as a preliminary step, but only as a secondary step after selection of cards based on another type of information such as the test compound, specific biological state of process acted on, test organism, etc.

27. Double coding in Fields W, X, and Y

In none of Fields W, X, and Y are two entries ever made. Field W may be coded with Symbol * along with any one of Symbols J through Q and Field Y may be coded with Symbol * or # along with any one of Symbols 0, A, and 1 through 9, but this is not double coding in the sense of coding a variable or a range of one type of information. The asterisk in Field W indicates an entirely different type of information than Symbols J through Q. When Symbol * is coded in Field W with any of Symbols J through Q or when Symbol * or # is coded in Field Y with any of Symbols 0, A, and 1 through 9, both symbols in the column are punched on the same IBM card in the column.